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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

Signature Page

Prepared by:

_____ Date: _____
PPD MPH, MS
PPD Biostatistics
Theradex Oncology

Reviewed by:

_____ Date: _____
PPD MS, PMP
PPD of Operations
Theradex Oncology

_____ Date: _____
PPD BS
PPD Statistical Programming
Theradex Oncology

_____ Date: _____
PPD
PPD
Theradex Oncology

Approved by:

PPD

_____ Date: 17 June, 2021
PPD
PPD
Medical Statistics, Bayer HealthCare Pharmaceuticals Inc.

Approved by:

PPD

_____ Date: 16 June, 2021
Dr PPD MD
PPD Darolutamide
Bayer HealthCare Pharmaceuticals Inc.

Statistical Analysis Plan

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Sponsor:	Bayer HealthCare Pharmaceuticals Inc. 100 Bayer Boulevard, Whippany NJ 07981-0915 USA
CRO:	Theradex Oncology 4365 Route 1 South, Suite 101 Princeton, New Jersey 08540 USA

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Abbreviations

AE	Adverse event
AESI	Adverse Event of Special Interest
ALT/SGPT	Alanine aminotransferase/ Serum glutamic-pyruvic transaminase
AST/SGOT	Aspartate aminotransferase/Serum glutamic-oxaloacetic transaminase
BFI	Brief Fatigue Inventory
bid	Twice daily
BUN	Blood urea nitrogen
CFR	Code of federal regulations
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
COWA	Controlled Oral Word Association
CRF	Case report form
CPM	Count per minute
CRPC	Castration-resistant prostate cancer
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic case report form
FACT-Cog	Functional Assessment of Cancer Therapy – Cognitive
FAS	Full analysis set
GCP	Good clinical practice
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
ICF	Informed consent form
ICH	International Council for Harmonization
IRB	Institutional Review Board
IWRS	Interactive web response system
KPS	Karnofsky Performance Scale
MCH	Mean corpuscular hemoglobin
MCID	Minimal clinically important difference
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
OS	Overall survival
PCWG	Prostate Cancer Working Group
PHQ-9	Patient Health Questionnaire-9
PSA	Prostate-specific antigen
PT	Preferred term
RBC	Red blood cell
RCI	Reliable change index
SAE	Serious adverse event
SAP	Statistical analysis plan
SoA	Schedule of activities
SOC	System Organ Class
SPPB	Short Physical Performance Battery
TEAE	Treatment-emergent adverse event
TMTA/TMTB	Trail Making Test Part A/B
TUG	Timed Up and Go
ULN	Upper limit of normal
WBC	White blood cell

1.0 Introduction

This Statistical Analysis Plan (SAP) describes analyses and data presentations for Bayer HealthCare Pharmaceuticals Protocol 20609. It provides details of the analysis populations, derived variables, and statistical methods to be used in the analyses and reporting of safety and efficacy data.

The purpose of the SAP is to ensure the credibility of the study findings by specifying the statistical approaches to study data analyses. This SAP will be finalized and signed prior to the clinical database lock for the final analyses. All statistical analyses detailed in this SAP are conducted using SAS statistical software (version 9.4 or higher).

1.1 Study Documents Used in the Preparation of this Document

The following documents were used in preparation of this SAP:

Study Document	Approval Date
Clinical Study Protocol	06 JUN 2019
20609-1180 Annotated eCRF Approval	17Sep2020
1180 Rave Annotated CRF Review	17Oct 2019

2.0 Objectives and Endpoints

Table 1 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 (CRPC).	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 from baseline, using the best TUG time out of the measured assessments during study visits. (The minimum clinically important difference [MCID] in TUG time is 1 second (Davies et al. 2016)) [1].
Secondary	
The secondary objectives of this study are to: • 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. • 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. • 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. • Compare the effects of treatment with darolutamide vs. enzalutamide on **cognitive function** as assessed by Hopkins Verbal Learning Test-Revised	**Physical Function:** • 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, using the best TUG time out of the measured assessments during study visits. • Time to worsening (increase of at least 1 second) in TUG time. • 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 one point worsening in SPPB total score from baseline. **Daily Activity:** • Mean change from baseline in daily physical activity at 12 and 24 weeks, and during the 24 weeks and 52 weeks from baseline. • Mean change from baseline in accelerometer-assessed proportion of time spent in light to vigorous physical activity (light physical activity defined as 100<AC per minute<760 and moderate-to-vigorous activity (≥760 AC per minute), at 12 and 24 weeks, and during the 24 weeks and 52 weeks from baseline. **Cognitive Function:** • 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 4 for the definition of decline for each test.

Objectives	Endpoints
(HVLT-R), Trail Making Test (TMT), Controlled Oral Word Association (COWA), and Functional Assessment of Cancer Therapy – Cognitive questionnaire (FACT-Cog).	• 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.
• Compare the effects of treatment with darolutamide vs. enzalutamide on **fatigue** as assessed by the Brief Fatigue Inventory (BFI).	**Fatigue:** • 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). • 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).
• Compare the effects of treatment with darolutamide vs. enzalutamide on **depression** as assessed by the Patient Health Questionnaire-9 (PHQ-9).	**Depression**: • 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.
• Evaluate **safety**, including AEs of special interest (AESI), of participants treated with darolutamide vs. enzalutamide.	**Safety** • All treatment emergent AEs (TEAEs), serious adverse events (SAEs), and AEs leading to study intervention discontinuation. • AEs of interest listed in section 5.5.3.
• Evaluate the effect of treatment with darolutamide or enzalutamide on prostate-specific antigen (PSA), survival status, and exposure.	**Exposure and other:** • Treatment exposure of the study intervention (defined as investigational intervention, protocol; Darolutamide or Enzalutamide) including time on treatment. • Dose reductions of study intervention. • Time to PSA progression (as per Prostate Cancer Working Group [PCWG3] criteria). • Survival status.

3.0 Study Design

3.1 Overall Study Design

This randomized, open-label, multicenter, Phase 2b study is designed to evaluate physical function, including balance and daily activity, in

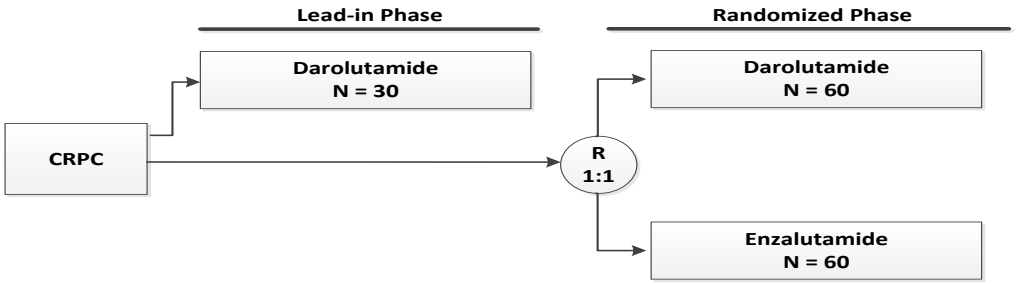
participants with CRPC, treated with darolutamide (or enzalutamide in randomized phase). It will also evaluate, safety, cognitive function, fatigue, and survival.

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. The lead-in phase analysis 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 will be conditional on the findings of the lead-in phase which will be reviewed with the members of the steering committee. Findings of the lead-in phase will determine feasibility to move on or not with a randomized phase. If determined feasible and decided to proceed with the randomized phase, the appropriate endpoint and the time point and time frame of evaluation of the endpoint for a randomized part of the study will be chosen and the sample size will be reassessed.

In the randomized 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 a decision is made based on the findings from the primary analysis of the lead-in phase as described above.

Figure 3–1: Study Periods



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

3.2 Blinding and Unblinding

This is an open-label study; blinding techniques are not required.

No formal interim analyses are planned in this study and a Data Monitoring Committee will not be utilized. However, 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.

3.3 Randomization and Stratification

Following the primary evaluation of the lead-in phase, approximately 120 additional patients will be randomized in a 1:1 ratio to receive either darolutamide (600 mg twice daily) or enzalutamide (160 mg once daily) using an Interactive Web Response System. Randomization will be stratified by age (<75, ≥75 years).

3.4 Sample Size

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 2. For instance, decline/worsening for TUG test is defined as an increase of at least 1 second in TUG time from baseline. The values are provided as a reference rather than a basis for decision making.

Table 2 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

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.

4.0 Management of Analysis Data

The data from all study centers will be pooled together for analyses. Participants will not be pooled across the two phases of the study, separate analyses will be performed for the lead-in phase and randomized phase.

4.1 Data Handling

Unscheduled laboratory results will not be analyzed for the visit summary of continuous values but will be included in the laboratory shift tables.

4.2 Missing Data

The primary endpoint is the Proportion of patients with worsening in TUG time from Baseline. Primary endpoint-related missing data will not be imputed, but a sensitivity analysis will be conducted by replacing missing TUG times with ≥ 1 second increase.

All missing or partial date will be presented in the patient listings, as they are recorded on the case report form, unless otherwise specified.

A conservative approach will be taken for partial or missing dates of AE and concomitant medications. Partial dates with missing day only will be imputed to either first of month, or first dose date if it falls in the same month. Partial dates with missing month will be imputed to either

January 1 or first dose date if it falls in the same year. Completely missing dates will be imputed using first dose date, unless the end date suggests it could have started prior to this in which case the imputed date will use 1st January of the same year as the end date. In all cases, imputed start dates must be compatible with reported end dates.

4.3 Coding Conventions for Events and Medications

Event/Medication	Coding/Mapping Convention
AE, Medical History Coding	MedDRA version 23.0 or higher
Lab Test Grade	NCI CTCAE version 5.0
Prior and Concomitant Medications	WHO DDE version 2020Mar or higher

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; NCI = National Cancer Institute; WHO-DDE = World Health Organisation Drug Dictionary Enhanced.

5.0 Statistical Methods

5.1 General

Demographic and baseline characteristics, efficacy assessments, and safety data will be summarized for the lead-in Phase and for the Randomization Phase separately. The Lead-in Phase summary will be based on a single group of subjects treated with darolutamide, while the Randomization Phase will be summarized by darolutamide, enzalutamide and overall groups. Unless otherwise stated, all analyses described below will be applied to both phases of the trial.

All variables will be analyzed with appropriate statistical methods. Continuous data will be presented as n, mean, standard deviation, median, quartiles, minimum, and maximum. Continuous variables will be described by absolute value and as change from baseline per analysis time point. Categorical data will be presented as frequency counts , percentages and 95% CI. All raw data collected will be listed.

5.1.1 Definitions

Baseline: The last measurements taken prior to first exposure to study drug, including Day 1 measurements taken pre-dosing. If patients have no value as defined above for a particular parameter, the baseline value will be missing.

5.1.2 Visit Window

In order to summarize longitudinal data per timepoint, assessments will be allocated to visits using pre-defined time windows. Unless otherwise specified, the Schedule of Activities and windowing in the protocol will be used. The deviations from visit windows specified in the protocol will be documented by site monitor in Monitor Express portal.

5.2 Study Populations

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

Table 3 Study Populations for Analyses

Population	Description
Enrolled	All participants who sign the ICF.
Full analysis set (FAS)	All enrolled participants or all randomized patients (for the randomized phase 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 phase 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 study treatment actually received. 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.

5.3 Study Population Characteristics

5.3.1 Study Enrollment

Patient enrollment, eligibility, and study populations are summarized by frequency and percentage of patients.

5.3.2 Patient Disposition

The disposition of patients (based on the reasons reported for treatment and study discontinuation) is summarized by frequency and percentage of patients.

5.3.3 Protocol Deviations

Protocol deviations are categorized by Theradex Oncology and Bayer HealthCare BioPharma as minor protocol deviations (a protocol deviation that does not have a significant impact on the research participant's rights, safety, or welfare; the integrity of the data; nor substantially alter risks to subjects as determined by IRB), and major protocol deviations (a deviation from the protocol, International Council for Harmonization Good Clinical Practice [ICH-GCP], or local requirements that may impact patient safety, affect the scientific integrity of the trial, or the patient's willingness to participate in the trial).

5.3.4 Prior Systemic Anti-Cancer Therapy

Prior systemic life prolonging anti-cancer therapies including treatment intent, the number of regimens (1, >=2) administered, best response, and discontinuation reason along with therapy types (Abiraterona acetate, prednisone, enzalutamide, apalutamide, darolutamide, docetaxel, bicalutamide, flutamide, nilutamide, Radium-223, sipuluecel-t, and systemic radiotherapy) as allowed based on exclusion criteria, will be summarized by frequency and percentage of patients within each category.

5.3.5 Prior Radiotherapy and Prior Surgery

Prior radiotherapy including intent, type, relieve skeletal symptom, irradiated location, best response, and prior surgeries will be summarized by frequency and percentage of patients within each category.

5.3.6 Demographics and Baseline Characteristics

Demographic data including age categories (<75, ≥75), sex, race, ethnicity, CRPC metastatic status and Karnofsky performance scale (KPS) are summarized by frequency and percentage of patients within each category.

Age is also summarized using descriptive statistics as a continuous variable. Dominant hand and education level are summarized by frequency and percentage of patients within each category.

5.4 Efficacy Analyses

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 being 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 being lost to follow-up, withdrawal, or death.

5.4.1 Primary Efficacy Endpoint Analysis

There is no primary efficacy endpoint in this study.

5.4.2 Secondary Efficacy Endpoint Analyses

The study is not powered to test a specific hypothesis for efficacy, the two arms will not be formally compared for efficacy.

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) are met. 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.

The SAS procedure, Proc Lifetest, will be used to calculate estimates of the time to PSA progression using Kaplan-Meier methodology. The Kaplan-Meier curves for the time to PSA progression will be presented. Confidence intervals (CIs) for the median duration times are calculated using the method by Brookmeyer and Crowley [2]. CIs for point estimates of the survival distribution are calculated using the method by Kalbfleisch and Prentice [3]. Patients who did not have a PSA progression event at the time of analysis (either for lead-in or randomization phase) will be censored at the date of the last assessment showing no evidence of PSA progression

PSA response at 24 and 52 weeks

Number (%) of subjects achieving 30% / 50% / 90% PSA reduction from baseline will be summarized for the time period up to and including each visit.

Overall survival (OS) 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 are still alive will be censored at the last date known to be alive. The Kaplan-Meier method will be used to estimate the median survival and survival rate at the 1-year timepoint along with the 95% CI for each treatment arm of the randomized phase (not to be analyzed in lead-in phase).

A listing of deaths on study or within 30 days post-last dose will also be produced.

5.4.3 Other

Additional subgroup analyses will be performed, as specified below.
Time to PSA progression and OS will be explored across baseline characteristic subgroups.

- Age group (< 75 vs. ≥ 75 years)
- Number of prior systemic life-prolonging anticancer therapies (1 vs. ≥ 2)

5.5 Safety and Tolerability Analysis

Safety analyses are based on the Safety population. Descriptive statistics are used to summarize the safety parameters. Safety data including AEs, AESI, laboratory parameters, vital signs, exposure and KPS. The protocol schedule of events and windowing will be used for the applicable safety table assessments.

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

5.5.1 Primary Endpoint Analyses

The primary variable in this study is the proportion of participants with a worsening in TUG time during the 24-week period from baseline, using the best TUG time out of the measured assessments during study visits (two or

three assessments). Worsening is defined as an increase of at least 1 second in TUG time from baseline.

The proportion of participants with a worsening in TUG time and the (exact) 95% CIs will be summarized by treatment arm. A comparison between treatment arms will be made using Cochran-Mantel-Haenszel (CMH) test adjusting for Age (<75, ≥75). A sensitivity analysis will be provided by replacing missing TUG times with ≥ 1 second increase. Primary endpoint (worsening in TUG) analysis will be performed by age (<75, ≥75), metastatic state (nmCRPC, mCRPC), Pain (yes, no pain), and opioid use (yes, no opioid use). Information on pain and opioid use will be retrieved from an examination of medical history and prior medication CRFs.

5.5.2 Secondary Endpoints Analyses

Physical function

- Proportion of participants with a worsening in TUG time from baseline at 12 and 24 week study visits, and at any time up to 52 weeks will be summarized.
- TUG time (secs) and percent change from baseline will also be summarized by metastatic/non-metastatic CRPC status, pain (yes, no pain), and opioid use (yes, no opioid use).
- At each assessment, status of TUG time will be summarized as the categories of improved, stable or worsened.
- Time to worsening 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 a worsening. Time to worsening in TUG time will be summarized using Kaplan-Meier methodology, and a comparison between the two arms in the randomization phase will be made using a two-sided, stratified log-rank test, stratified by Age (<75, ≥75). 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. The Kaplan-Meier plots will be provided for both stratified and unstratified analyses.
- Similar to the primary endpoint, the proportion of participants with a decline of at least 1 point in SPPB total score at 12 and 24 week study visits and at any time up to 24 and 52 weeks will be summarized. SPPB

will be analyzed by age (<75, ≥75), metastatic state (nmCRPC, mCRPC), Pain (yes, no pain), opioid use (yes, no opioid use).

Daily Activity

- Descriptive statistics on mean change and percent change from baseline in daily activity, measured as counts per minute (CPM), will be provided for both lead-in at 12 and 24 weeks and randomization phase at 12, 24 and 52 weeks. Subjects must provide at least 2 out of 7 days of data prior to the visit, each day containing ≥10 awake hours, to be considered eligible for analysis. For each epoch, counts from the X, Y and Z axes will be converted to a single measure per the vector magnitude =

$$\sqrt{(axis\ 1)^2 + (axis\ 2)^2 + (axis\ 3)^2}$$

  CPM for each valid day is defined as 'awake wear-filtered total vector magnitude counts' divided by 'awake wear minutes'. A subject's CPM at each visit is the average of daily CPM.
- CPM will also be analyzed by age (<75, ≥75), metastatic state (nmCRPC, mCRPC), pain (yes, no pain), and opioid use (yes, no opioid use) in both phases. In the randomization phase, model-based least squares means on percent change from baseline in CPM will be reported for treatment group, adjusting for baseline CPM, age (<75, ≥75), metastatic state (nmCRPC, mCRPC), pain (yes, no pain) and opioid use (yes, no opioid use).
- Because of the skewed nature of CPM data, summary statistics will also be provided for log-transformed CPM. For summary statistics by visit, calculations are done on the log scale, and then back-transformed at the end. For % change from baseline, the back-transform for (LS)mean (95% CI) = 100 × [exp((LS)mean change from baseline (95% CI) in natural logarithm) – 1].
- For the randomization phase, treatment arms will be compared at each visit using 2-sample t-test, mean change difference (SE), 95% CI and p-value of darolutamide vs. enzalutamide will be provided.
- The percentage of time at each visit that CPM fall into the following categories will be summarized for the lead-in phase: Sedentary (0-99), Light (100-1951), Moderate (1952-5724), Vigorous (5725-9498), Very vigorous (9499-∞). Also mean change and percentage change from

baseline will be summarized for percentage of time spent in each of the aforementioned categories.

Cognitive function

- The proportion of participants with a decline in cognitive function at 24 and within 52 weeks as assessed by HVLT-R, TMT, and COWA, will be summarized. 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. The proportion of participants with a decline and exact 95% CIs will be summarized. For the randomization phase, the proportion of subjects with a decline will be summarized separately by treatment arm, and a comparison between arms at week 24 and week 52 will be made using CMH test adjusting for Age (<75, ≥75).

Test	**Reliable Change Index threshold (from baseline)**
Hopkins Verbal Learning Test - Revised Total Recall (HVLT-R TR)	±5 words HVLT-R TR has a range of 0-36, recalling a list of 12 words over 3 trials.
Hopkins Verbal Learning Test - Revised Delayed Recall (HVLT-R DR)	±3 words HVLT-R DR has a range of 0-12.
Hopkins Verbal Learning Test - Revised Delayed Recognition (HVLT-R RECOG)	±2 words HVLT-R RECOG has a range of -12 to 12 words. It is equal to true positives (subject says 'yes' to 12 original words on list) minus false positives (subjects says 'yes' to distractors [12 words not on original list]).
Trail Making Test: Part A (TMTA)	±12 seconds TMT Part A is timed up to a maximum of 3 minutes. If not completed in the given amount of time, the subject is assigned a time equal to the maximum time.
Trail Making Test: Part B (TMTB)	±26 seconds

	TMT Part B is timed up to a maximum of 5 minutes. If not completed in the given amount of time, the subject is assigned a time equal to the maximum time.
Controlled Oral Word Association (COWA)	±12 words Subjects are asked to name as many words as possible all beginning with a specified letter. A total of three trials are administered, and the score on the COWA is the total number of words named across the three trials.

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

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) within the first 24 weeks, and during the entire 52 week period will be summarized. Exact 95% CI will also be presented, and a comparison between arms will be made using CMH test adjusting for Age (<75, ≥75) for the randomization phase.
- Similarly, the proportion of participants with an increase of at least 1 point 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, and for the randomization phase proportions will be reported by treatment arm. A comparison between arms will be made using a CMH test adjusting for Age (<75, ≥75).

Depression

The proportion of participants with a worsening of scores by PHQ-9 within the first 24 weeks and during the entire 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.

5.5.3 AE, Exposure and Other

- AEs, drug-related AEs, and SAEs will be summarized in number (%) of patients.
- AEs of interest (Bone fractures, Diabetes mellitus and hyperglycemia, Fall, Fatigue/ asthenic conditions, Weight loss, Interstitial lung disease, Rash, Seizure, Hypertension, Mental impairment disorders, Depressed mood disorders, Breast disorders/gynecomastia, Cardiac disorders, Coronary artery disorders, Cerebral ischaemia, Cerebral and intracranial hemorrhage) will be summarized descriptively.
- Time to deterioration of KPS will be calculated as the time from randomization (or time from first dose in the lead-in phase) to the first date the patient had a decline in KPS of at least 10 points. In the event of no deterioration of KPS, the time to deterioration of KPS will be censored at the last evaluable assessment. Time to deterioration of KPS will be analyzed and presented the same way as the time to PSA progression.
- Treatment exposure of the study intervention, including time on treatment and dose changes, will be summarized.

Table 4 Study Assessments for Physical Ability and Cognitive Function

Test	Description	Possible Range of score	MCID/RCI from Baseline
Physical ability tests			
Timed Up and 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. Where possible, TUG time is to be measured by independent blinded assessors.	>1 second	1 second (Davies et al. 2016) [1]
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 (Davies et al. 2016) [1]
Cognitive Tests			

Test	Description	Possible Range of score	MCID/RCI from Baseline
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 (Wefel et al. 2011) [4]
Hopkins Verbal Learning Test-Revised **Delayed Recall** **(HVLT-R DR)**	Spontaneous recall is assessed before and after a delay.	0–12 words	±3 words (Wefel et al. 2011) [4]
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 (Wefel et al. 2011) [4]
Trail Making Test (TMT) **Part A (TMTA)** **Part B (TMTB)**	The 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. TMTB includes a divided attention component requiring mental flexibility (i.e., executive function). On this subtest, dots with numbers and letters are randomly scattered on the test page. Participants are required to alternate between connecting numbers and letters in an ascending sequential order. 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.	1–2750 seconds 1–3750 seconds	±12 seconds ±26 seconds (Wefel et al. 2011) [4]
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,	0 – unlimited words	±12 words (Wefel et al. 2011) [4]

Test	Description	Possible Range of score	MCID/RCI from Baseline
	each with three unique letter exemplars.		
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 in cancer patients. It is a patient-reported outcome measure used to assess cognitive function in patients undergoing cancer therapy.	0–72 points	6.9-10.6 points (Cheung et al. 2014, Costa et al. 2018) [5]

Note: 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; RCI = reliable change index; SPPB = Short Physical Performance Battery; TMTA/TMTB = Trail Making Test Part A/B; TUG = Timed up and Go

5.5.4 Treatment Exposure and Compliance

Study drug (Darolutamide / Enzalutamide) exposure and compliance will be summarized using descriptive statistics. The summary of treatment exposure will include number of cycles, duration of treatment, total actual dose and total intended dose. Duration of Exposure is defined as the duration between the first and last dose of treatment (last dose date - first dose date+1). Total Actual Dose is defined as the sum of all treatment administered over the entire course of the study. Total Intended Dose is defined as the sum of intended doses during the duration of exposure, based on no modifications to dose or schedule. Percent Compliance is defined as the Total Actual Dose divided by Total Intended Dose multiplied by 100% for each patient. The frequency and percentage of patients receiving <100%, 100%, and >100% of their dose compliance are summarized.

The number of patients with dose reductions, increased, interrupted and withdrawn (along with their reasons) are all summarized using frequency counts and percentages, for patients that received darolutamide or enzalutamide.

5.5.5 Adverse Events

A TEAE is defined as any event arising or worsening after first dose study drug until 30 days after last dose. If an AE occurs before the first dose of treatment it will be considered a non-treatment emergent AE.

TEAEs and AEs will be summarized by frequency and percentage of patients and tabulated by MedDRA system organ class (SOC) and preferred term (PT), by maximum NCI-CTCAE version 5.0 grade and by drug relationship as not related and related to treatment. SAEs, TEAEs leading to treatment discontinuation and deaths will be summarized. Drug-related TEAEs by CTCAE grade, and drug-related grade 3 or higher TEAEs are summarized. Patients with multiple TEAEs or AEs are counted once within a summary category-SOC, PT, maximum grade, or relationship to treatments.

AESI be summarized by SOC and PT and grade in separate summary tables. All AEs will be listed.

5.5.6 Laboratory Data

Laboratory data are summarized by laboratory tests for the treatment period, defined as the time from first dose up to 30 days post last dose of treatment. Laboratory data are converted to SI units prior to summarization. All laboratory tests are provided in patient data listings. The listings indicate the normal ranges for each parameter. Each value, if appropriate, is classified as falling above (H), below (L), or within normal range and also graded using the CTCAE criteria.

The observed data and change from baseline are summarized at each of the laboratory timepoints, using descriptive statistics, for hematology, chemistry and urinalysis laboratory tests.

The changes from baseline to maximum CTCAE grade during treatment are summarized by frequency and percentage of patients using shift tables for every gradable hematology and chemistry tests. Maximum CTCAE Grade is defined as the highest CTCAE version 5.0 grade reported during the treatment period.

A listing of patients with grade 3 or 4 laboratory values during treatment period is also provided.

5.5.7 Other Safety Parameters

Vital signs, including blood pressure, pulse rate, and temperature, as well as weight and height are summarized using descriptive statistics.

5.5.8 Concomitant and Prior Medications

Prior and Concomitant medications are coded using the World Health Organization Drug Dictionary Enhanced (WHO-DDE version 2020Mar or higher), tabulated by drug class and term, and summarized by frequency and percentage of patients. Patients are counted only once in each summary category (e.g. drug class or term).

Prior medications are defined as medications taken within 12 weeks and stopped before treatment Day 1. Concomitant medications are defined as ongoing at treatment Day 1 or taken on Day 1 or thereafter up to the last dose of treatment plus 30 days. Prior and concomitant medications are summarized within each category separately and listed.

6.0 Changes to Planned Analyses

Not applicable.

7.0 References

[1] Davies CC, Colon G, Geyer H, Pfalzer L, Fisher MI. Oncology EDGE Task Force on Prostate Cancer Outcomes: A Systematic Review of Outcome Measures for Functional Mobility. Rehabil Oncol. 2016;34(3):82-96

[2] Brookmeyer R Crowley J. A confidence interval for the median survival time, Biometrics 1982;38:29-41.

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[4] Wefel JS, Cloughesy T, Zazzali JL, Zheng M, Prados M, Wen PY, et al. Neurocognitive function in patients with recurrent glioblastoma treated with bevacizumab. Neuro Oncol. 2011 Jun;13(6):660-8

[5] Cheung YT, Foo YL, Shwe M, Tan YP, Fan G, Yong WS, et al. Minimal clinically important difference (MCID) for the functional assessment of cancer therapy: cognitive function (FACT-Cog) in breast cancer patients. J Clin Epidemiol. 2014 Jul;67(7):811-20

8.0 Table 8-1 Schedule of Activities

Lead-in phase

Table 8–1 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	

Table 8–1 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
Serum PSA [a]	X	X	X		X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	
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 Protocol 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 Protocol Section 4.4.2).

Randomized Phase

Table 8–2 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 8–2 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 Protocol 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 Protocol Section 4.4.2).

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