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Title Page

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

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Acronym: ARANOTE

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Version History

SAP Version	Date	Change	Rationale
1.0	17 APR 2024	Not applicable	Original version
2.0	26 JUN 2024	Section 2.1 and Section 4.2.1.	More details for final analysis of OS are added. Additional rules to cover specific scenarios for rPFS calculation are added to handle the different scenarios of data collection (e.g. bone assessment stopped earlier than soft tissue assessment).
		Section 4.3.4	Time period for PSA assessment is added.

List of Abbreviations

ADT	Androgen deprivation therapy
AE	Adverse event
AEE	Actual extent of exposure
ALP	Alkaline phosphatase
ATC	Anatomical-Therapeutic-Chemical
BPI-SF	Brief Pain Inventory – Short Form
CI	Confidence interval
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
CV	Coefficient of variation
DILI	Drug-induced liver injuries
DMC	Data Monitoring Committee
EAIR	Exposure adjusted incidence rate
EBRT	External beam radiation therapy
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EOT	End of treatment
FAS	Full analysis set
FACT-P	Functional Assessment of Cancer Therapy-Prostate
GCP	Good Clinical Practice
HR	Hazard ratio
HRQoL	Health-related Quality of Life
ICF	Informed consent form
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LHRH	Luteinizing hormone releasing hormone
LKAD	Last known alive date
MedDRA	Medical Dictionary for Regulatory Activities
mHSPC	Metastatic hormone-sensitive prostate cancer
MRI	Magnetic resonance imaging
NACT	New anti-cancer therapy
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events;
OS	Overall survival
PCWG3	Prostate Cancer Clinical Trials Working Group
PFS	Progression-free survival
PRO	Patient-reported outcomes
PSA	Prostate-specific antigen
PSAUR	PSA undetectable rate
PT	Preferred Term
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	Radiological progression-free survival
SAE	Serious adverse event
SAF	Safety analysis set
SD	Standard deviation
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SSE	Symptomatic skeletal event
TEAE	Treatment emergent adverse events
TESAE	Treatment emergent serious adverse events
TURP	Transurethral Resection of the Prostate
ULN	Upper limits of normal
TTPP	Time to pain progression
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary
WPS	Worst pain subscale

1. Introduction

Study 21140 (ARANOTE) is a multinational, randomized, double-blind, placebo-controlled, Phase 3 efficacy and safety study of darolutamide in addition to standard androgen deprivation therapy (ADT) versus placebo plus ADT in men with metastatic hormone-sensitive prostate cancer (mHSPC).

This statistical analysis plan (SAP) for Study 21140 contains definitions of analysis sets, derived variables, and describes the statistical methods for the analysis of efficacy and safety to be included in the clinical study report for Study 21140.

This SAP is based on protocol amendment 1 (v. 2.0), dated 28 JUN 2022.

1.1 Objectives, Endpoints, and Estimands

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

All the objectives listed in Table 1–1 will be analyzed at the primary completion.

Table 1–1 Objectives and Endpoints

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

* Not applicable for China.

Primary estimand

Scientific question of interest:

What is the treatment effect based on radiological progression-free survival (rPFS) for darolutamide in addition to ADT vs. placebo plus ADT in participants with metastatic hormone-sensitive prostate cancer (mHSPC), regardless of study treatment discontinuation?

Treatment: Darolutamide (BAY 1841788) 600 mg twice daily (BID) vs. Placebo matching darolutamide

Population: Randomized participants as defined by the protocol inclusion/exclusion criteria

Variable: rPFS assessed by central review based on RECIST v. 1.1 criteria for soft tissue metastases and PCWG3 criteria for bone metastases

Intercurrent events and Strategy:

Intercurrent event	**Strategy for addressing intercurrent event**
Early discontinuation of study treatment	Treatment policy strategy: time to PD or death, regardless of whether or not study treatment discontinuation had occurred.
Start of subsequent anticancer therapy	Hypothetical strategy: participants with rPD or death after subsequent anticancer therapy are censored at the last disease assessment showing no evidence of PD before the use of subsequent anticancer therapy. (Due to no tumor assessment collected after start of subsequent anticancer therapy per protocol)

Population-level summary: rPFS will be analyzed with log-rank test and Cox regression proportional hazard model, stratified by the same factor as used for randomization.

Secondary estimand

Scientific question of interest:

What is the treatment effect based on overall survival (OS) for darolutamide in addition to ADT vs. placebo plus ADT in participants with mHSPC, regardless of study treatment discontinuation or start of subsequent anticancer therapy?

Treatment: Darolutamide (BAY 1841788) 600 mg BID vs. Placebo matching darolutamide

Population: Randomized participants as defined by the protocol inclusion/exclusion criteria

Variable: OS is defined as the time from the date of randomization to the date of death from any cause

Intercurrent events and Strategy:

Intercurrent event	Strategy for addressing intercurrent event
Early discontinuation of study treatment	Treatment policy strategy: time to death, regardless of whether or not study treatment discontinuation had occurred.
Start of subsequent anticancer therapy	Treatment policy strategy: time to death, regardless of whether or not the subsequent anticancer therapy had occurred.

Population-level summary: OS will be analyzed with log-rank test and Cox regression proportional hazard model, stratified by the same factor as used for randomization.

1.2 Study Design

Design overview

Approximately 665 participants who meet the eligibility criteria including confirmation of metastatic disease by central review will be randomized in a 2:1 ratio to receive one of the following study drugs:

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

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

Participants will be stratified at randomization as follows:

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

The study comprises 4 consecutive periods: Screening, Treatment, Active Follow-up, and Long-term (survival) Follow-up.

Screening period:

All trial-related procedures and evaluations will only be performed after the participant has agreed to participate and has signed the informed consent form (ICF).

The Screening period will consist of multiple evaluations that will take place within 28 days prior to randomization to ensure that all eligibility criteria are met. Once eligibility is properly documented, eligible participants will be randomized in a ratio of 2:1 to treatment with darolutamide or placebo.

Treatment period:

The start of the Treatment period is defined by the first administration of study drug.

During treatment period, participants will be evaluated with regular clinic visits every 12 weeks (±7 days) for efficacy and safety.

In the double-blind period, participants will receive study drug until documented radiological disease progression assessed by central review, unacceptable toxicity or until any other withdrawal criteria is met.

An independent Data Monitoring Committee (DMC) will monitor the unblinded safety data on a regular basis throughout the double-blind period.

Active follow-up period:

The Active follow-up period is the interval from the end-of-study drug intake to the end of all protocol-specified post-treatment assessments. Participants who discontinued study drug will enter in the Active follow-up period. The Active follow-up period extends from the discontinuation of treatment period for approximately 1 year (12 ± 1 months) or until the participant can no longer travel to the clinic, dies, is lost to follow-up, or withdraws informed consent. It includes the end of treatment (EOT) visit and Active follow-up visits.

An EOT visit will be conducted 30 days (+7 days) after the last dose of study drug. During the EOT visit, procedures to monitor participant's health, to identify potential toxicities, and to assess efficacy will be performed.

Long-term (survival) Follow-up period:

After completing the Active follow-up period, participants will enter the Long-term follow-up period and will be contacted approximately every 12 weeks (by telephone).

Survival sweep:

For the primary analysis and subsequent overall survival (OS) analyses, the survival status will be collected through a survival sweep. All participants considered alive at the database cut-off date for the primary analysis and prior to the subsequent analysis of OS will be contacted for survival status to ensure data are complete up to the database cut-off date.

Primary completion

The analysis of rPFS will be performed when approximately 214 events of rPFS have been observed by central review.

After primary completion

A final analysis of OS and safety, including data collected after primary completion, will be performed at a later time point. The hypotheses of other secondary endpoints might be tested again using data collected until primary completion and based on the schema stated in Section 2.1, which will be determined after the primary completion analysis.

2. Statistical Hypothesis

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

2.1 Multiplicity Adjustment

Secondary efficacy endpoints (OS, Time to initiation of subsequent anticancer therapy, Time to CRPC, Time to PSA progression, PSA undetectable rates and Time to pain progression) will be tested for statistical significance with the hierarchical gatekeeping procedure. The order of testing for statistical significance is as follow:

- Overall survival (OS)
- Time to initiation of subsequent anti-cancer therapy
- Time to castration-resistant prostate cancer (CRPC)
- Time to PSA progression
- PSA undetectable rates
- Time to pain progression

Secondary efficacy endpoints will be tested only if the primary endpoint rPFS is statistically significant at a one-sided alpha level of 0.025. If rPFS is not significant, all secondary efficacy endpoints will be considered as not significant. The same overall one-sided alpha 0.025 (equivalent two-sided alpha 0.05) as used for rPFS will be used for the secondary endpoints. They will be tested according to the sequence given above. If the previous endpoint in the hierarchy is significant, then the next endpoint in the order will be tested. If the prior endpoint in the order is not significant, then the next endpoint in the order will not be tested and this and all subsequent secondary endpoints will be considered as not significant.

The OS endpoints will be tested at two time points, an interim and a final analysis. The interim analysis of OS will occur on the same locked database (with the same data cutoff date) as the analysis of the primary endpoint rPFS. The final OS analysis will occur when approximately 180 OS events has been observed. Alpha levels (α1, α2) for the two OS analyses will be calculated with an O'Brien-Fleming alpha-spending function based on the actual number of OS events observed up to the primary data cut-off dates, and the planned OS events at final analysis. Table 2–1 shows an example of approximate on-sided nominal alpha (α) and standard normal significance thresholds (z), assuming number of OS events of 145 at interim and 180 at the final OS analysis. This table will be updated using the actual number of OS events at the interim OS analyses.

Table 2–1 Schema for one-sided nominal alpha and standard normal thresholds z for OS

Number of events	**Interim analysis** α1, z1	**Final analysis** α2, z2
145 events at interim	0.0125, -2.241	
180 events at final		0.0216, -2.0265

After OS is statistically significant at either interim or final analysis, all other secondary endpoints will be tested based on the same data observed at primary completion (i.e., even if these endpoints are tested at the time of the final OS analysis, data used for testing them will be the same as at the primary rPFS analysis), and one-sided alpha 0.025 will be used for these other secondary endpoints (at either the interim or final OS analysis, depending on when OS is statistically significant).

3. Analysis Sets

Populations for analyses are defined in Table 3–1.

able 3–1 Populations for analyses

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

Abbreviations: ICF = Informed consent form

Safety data will be analyzed as treated:

- Participants will be included in the darolutamide arm if they received any dose of darolutamide
- Participants will be included in the placebo arm if they received placebo only (i.e., not any dose of darolutamide)

4. Statistical Analyses

4.1 General Considerations

4.1.1 General principles

The statistical evaluation will be performed by using the software SAS (release 9.4 or higher; SAS Institute Inc., Cary, NC, USA).

Descriptive summaries will be presented by treatment arm and overall for all variables. The number of non-missing observations (n), mean (Mean), standard deviation (SD), minimum (Min), quartiles, median (Median), and maximum (Max) will be provided for metric data.

Categorical data will be summarized using frequency counts and percentages as well as the number of values used in the denominator used for the calculation of the percentages. Where applicable, these summaries will be provided by visit.

For time-to-event analyses the censoring mechanism is assumed to be non-informative. Participants without events will be handled as right-censored in time-to-event analyses. Time to event will be calculated in days as date of event or censoring minus date of randomization and presented in months (days/30.44). If event or censoring date is on date of the randomization, then time to event =1 (or day 1). In all summaries, change from baseline variables will be calculated as the post treatment value minus the value at baseline. The percentage change from baseline will be calculated as (postbaseline value - baseline value) / baseline value x 100.

All data will be presented in the participant data listing as they are recorded on the Case Report Form (CRF), i.e., partially missing data will appear as such.

Definition of efficacy and safety endpoints, analyses strategies, structure of analyses datasets and layout of analyses data displays are following Bayer standards as documented in the Bayer standard systems Global Medical Standards and Oncology Therapeutic Area Standards, where the given ordering reflects the priority of the different standards, meaning specifications of the latter ones have to be followed only if not specified in standards mentioned before. Study-specific specifications may be included in addition to the project standards, if needed.

In the absence of any impact on primary efficacy endpoint (e.g., data quality, dropout rate, tumor assessment schedule etc.) on participants arising from the Ukraine-Russia conflict at primary completion, participants from Ukraine and Russia will not be excluded from analyses, neither additional method will be considered to handle the data of these participants for the primary analysis.

4.1.2 Data rules

Baseline

Baseline data will be taken from the last non-missing observation on or before the first day of study intervention intake. For the patients who have been randomized but not treated, baseline data will be taken from the last non-missing observation on or before the randomization.

Repeated measures

If there are repeated measurements per time point on the same day (e.g., laboratory values, vital signs, etc.), the following rules will be used (unless otherwise specified):

- Before the start of the study drug administration (i.e., for screening and baseline value), the latest measurement at scheduled visits will be used. Unscheduled visits will be used if there are no measurements at scheduled visits. If the latter is the case, the last unscheduled visit will be used.
- In case of repeated measurements at any post baseline time point, the first measurement at scheduled visits will be used unless otherwise specified. Unscheduled visits will be used if there are no measurements at scheduled visits. If the latter is the case, the first unscheduled visit will be used.

Stratification variables

IWRS stratification factors as used for randomization:

- Visceral disease (present versus absent)
- Prior local therapy (Yes versus No), including prostatectomy, radiotherapy on the prostate, orchiectomy, biopsy, etc.

The primary stratified efficacy analyses will be based on the information collected in the IWRS.

BPI-SF

The BPI-SF is completed daily over a 7-day period. The forms at the planned time point for assessment is considered as valid if:

- The forms were completed 7+1 days before and/or on the date of planned time point for assessment, and
- In the case that the form was completed daily during the 7+1 days period, then the forms completed during the last 7 days before and/or on the first day of study intervention or the first 7 form of each planned time point for assessment (except for visit 1)

The WPS, the pain severity and the pain interference will be calculated using the mean score of the valid forms during the 7-day period. The earliest date of the valid forms during the 7-day period will be used for the date of the planned time point for assessment. If more than one form was done on the same day, then the mean score will be used for this day.

4.1.3 Handling of Dropouts

Screen Failures

A participant who consented to participate in the clinical study but is not subsequently assigned to study treatment is defined as a screen failure. Individuals assessed for eligibility who do not meet the criteria for participation in this study (initial screen failure) may be rescreened. Rescreened participants may be assigned a new participant identification (ID) number. For other reporting purposes, the participant will be identified by the most recent participant ID, and the reported date of informed consent will be the initial informed consent date. Only the last enrolment of re-screened participants will be reported.

Dropout

A participant who discontinues rPFS efficacy evaluation before database cut-off date and without a rPFS event is defined as a “dropout” and will not be replaced.

Withdrawal

Withdrawal from the study treatment alone does not constitute withdrawal from the study. A participant who withdraws from the study treatment for any reason is to be encouraged to remain on the study for follow-up of primary, secondary, and other objectives (i.e., continue in the applicable Active follow-up and/or Long-term follow-up periods). A participant is expected to participate in follow-up unless they explicitly object.

Withdrawal from each study period (Screening, Treatment period, Active follow-up, Long-term follow-up) is recorded in the eCRF separately, and will be reported separately, with separate reasons for withdrawal reported for each.

4.1.4 Handling of Missing Data

In order to achieve the goal of a well conducted clinical trial according to Good Clinical Practice (GCP), every effort should be made to collect all data. However, despite best efforts, it may be inevitable that missing or incomplete data are reported. All missing or partial data will be presented in the participants’ data listing as they are recorded on the Case Report Form. Except as noted, missing data will not be estimated or carried forward in any statistical analysis.

When appropriate, the following rules will be implemented so as not to exclude participants from statistical analyses due to missing or incomplete data:

Study treatment start and end dates

Imputation will be done for partially missing start date of study treatment administration as follows:

- If partial date has day and month missing, then date will be imputed as the randomization date.
- If partial date has missing day only, then the first day of the month will be assigned to the missing day.
- If the imputed first day of the month is before the randomization date, then the date will be imputed as the randomization date.

Imputation will be done for partially missing end date of study treatment administration as follows:

- If complete date is missing, then the end date is considered as missing, no imputation will be performed.
- If partial date has day and month missing, then date will be imputed as the last day of the last month will be assigned to the missing day.
- If partial date has missing day only, then the last day of the month will be assigned to the missing day.

Time-to-event endpoints

Every effort should be made to resolve incomplete or missing dates during the course of the study (i.e., edit checks, data cleaning/monitoring etc.). However, in rare circumstances, missing parts of either the censoring date or the event date may occur where an imputation algorithm has to be defined. In general, the following rule should be followed: Missing month or year is not acceptable for all time-to-event endpoints. If only day is missing, the following imputation will be applied: for missing day, day 15 of the month will be used; This applies to all time-to-event endpoints dates if the dates are partially missing in the selected data panels, unless other specified. If the imputed date is after the date of withdraw inform consent, day 1 of the month will be used for the missing day.

Questionnaires

In this study, the Brief Pain Inventory – Short form (BPI-SF) (Appendix 8.48.4) is used. The items are aggregated into two dimensions: pain severity score and pain interference score. All 4 severity items (questions 3 to 6 from the BPI-SF) must be completed to estimate the pain severity score, if one or more out of the four items (questions 3 to 6 from the BPI-SF) are missing then the pain severity will be set to missing. The pain interference score will be set to missing if four or more out of the seven items (item 9A-9G in the BPI-SF) are missing.

FACT-P total score is the sum of subscale scores. If less than or equal to 50% of the items are answered for any subscale, then the score of that subscale is set to missing. The total score is then calculated as the sum of the non-missing subscale scores. Moreover, the FACT-P total score is set to missing if the related overall item response rate is less than or equal to 80% or any subscale score is missing.

Safety Variables

Incomplete adverse event/concomitant medication / radiotherapy / procedure start and end dates will be imputed according to Appendix 8.8. The end date of procedure will be same as

the start date in the case of incomplete procedure end date.

The imputed dates will be used to assess whether AEs should be considered as treatment emergent.

Laboratory Assessments

If laboratory assessment results contain an inequality sign "<" or ">", then the laboratory assessment values reported with "<" will be imputed to 90% of the reported threshold, and the laboratory assessment values reported with '>' will be imputed to 110% of the reported threshold, the imputed laboratory assessment values will be used for both safety and efficacy analyses.

4.2 Primary Endpoint Analysis

4.2.1 Definition of Endpoint(s)

The primary endpoint rPFS uses conventional imaging method (99mTc-phosphonate bone scan, CT/MRI scan). rPFS is defined as the time from the date of randomization to the date of progressive disease in malignant soft tissue lesions, progressive disease in malignant bone lesions, or death due to any cause, whichever occurs first. Malignant soft tissue lesions will be assessed by RECIST 1.1 criteria (1) (Appendix 8.1) and malignant bone lesions will be assessed by PCWG3 criteria (2) (Appendix 8.28.2). The data from central review will be used for the primary analysis. The censoring rules are specified in Table 4–1. Progressive disease in soft tissue lesions and bone lesions will be evaluated separately, the censoring rules will be applied separately to the bone tumor assessment and soft tissue tumor assessment based on conventional imaging.

rPFS is calculated as 'the earliest date of first documentation of radiological progressive disease in soft tissue or bone, or death due to any cause minus randomization date'.

rPFS for soft tissue and bone will be calculated separately first, incorporating death as an event as applicable. Subsequently the soft tissue and the bone rPFS will be combined to obtain the overall rPFS. If both are censored overall rPFS will be censored at the smaller value. If there is an event only in the soft tissue or bone rPFS and the event occurs later than the censored value from the other rPFS :

- If the gap between the event and the other rPFS censored value is $> (24+1)$ weeks the overall rPFS will be censored and its value will be the smaller of the two individual component rPFS values.
- If the gap between the event and the other rPFS censored value is $\leq (24+1)$ weeks the overall rPFS will be an event and its value will be the larger of the two individual component rPFS values.

Two independent central primary readers will review each time point and provide their assessment. In case the two primary readers results at the same timepoint do not match, the adjudication process will start, meaning that a third reviewer will review the scans, will agree with one of the primary readers and the results agreed by adjudicator will be used for the analysis. In case the two primary readers' results match and no adjudication process triggers, the result of central reviewer 1 will be selected for the analysis of response.

Table 4–1 Censoring rules for rPFS

Situation	End Date	Censored	Reason for Censoring
Radiological progression	Date of documented progression	No	NA
Death without radiological progression and within (24+1) weeks after the last adequate* scan	Date of death	No	NA
Without any post-baseline tumor assessments and death within (24+1) weeks after randomization	Date of death	No	NA
No baseline tumor assessment and death within 24+1 weeks after randomization	Date of death	No	NA
Without radiological progression or death	Date of last adequate* tumor assessment before discontinuation	Yes	No documented radiographic progression or death
Without any post-baseline tumor assessments and died later than (24+1) weeks after randomization	Date of randomization	Yes	Assigning a rPFS event after this wide assessment gap would have too much uncertainty regarding the true date of the event, as there could have been an earlier radiological progression event.
Radiological progression occurs later than (24+1) weeks of last adequate* scan (24-weeks is based on 2 protocol specified tumor assessment time intervals, one week added for the protocol allows one week window for a given tumor assessment)	Date of last adequate*tumor assessment before radiological progression	Yes	Assigning a rPFS event after this wide assessment gap would have too much uncertainty regarding the true date of the event, as there could have been an earlier radiological progression event.
Death without radiological progression and later than (24+1) weeks of last adequate* scan (24-weeks is based on 2 protocol specified tumor assessment time intervals, one week added for the protocol allows one week window for a given tumor assessment)	Date of last adequate* tumor assessment	Yes	Assigning a rPFS event after this wide assessment gap would have too much uncertainty regarding the true date of the event, as there could have been an earlier radiological progression event.

Situation	End Date	Censored	Reason for Censoring
No baseline tumor assessment and no death within 24+1 weeks after randomization	Date of randomization	Yes	Not possible to document that there is a rPFS event or is no rPFS event at any post-randomization date
Without any post-baseline tumor assessments and no death within 24+1 weeks after randomization	Date of randomization	Yes	Not possible to document that there is a rPFS event or is no rPFS event at any post-randomization date
Subsequent anticancer therapy started prior or without radiological progression or death	Date of last adequate*tumor assessment before or on start of new anti-cancer treatment	Yes	Any censoring or event at a date after start of subsequent anticancer therapy would be under the influence of the subsequent therapy and therefore no longer reflects the study treatment in an unbiased way

* a timepoint with overall response of CR, PR, SD, Non-applicable, PDu or non-CR/non-PD will be considered adequate.

4.2.2 Main Analytical Approach

The primary estimand is prescribed in Section 1.1. The rPFS analysis will be performed based on FAS when approximately 214 events have been observed.

The comparative analysis of rPFS will be a one-sided type I error of 0.025 stratified log-rank test, with the same IWRS stratification factors as used for randomization: visceral disease (present versus absent), prior local therapy (Yes versus No). If the p-value from the one-sided log-rank test is less than 0.025 together with the HR less than 1, the null hypothesis will be rejected in favor of the alternative hypothesis.

The SAS code will be similar to the following:

PROC LIFETEST DATA=<DATASET>;

*TIME EFFVAL * CENSORNY;*

STRATA {strata variables} / GROUP=TREATMGR test=(logrank);

RUN;

The HR of darolutamide over placebo for rPFS and its 95% confidence interval (CI) will be calculated using the Cox model, stratified by the same factors as stated above. The SAS code similar to the following will be used:

PROC PHREG DATA = <DATASET>;

*MODEL EFFVAL * CENSORNY = TREATMGR;*

STRATA {strata variables};

RUN;

Kaplan-Meier (KM) estimates for the median time (including 95% CI) and first and third quartiles will be presented for each treatment arm. The KM estimates of rPFS rates at time points such as 3 months, 6 months, etc., together with corresponding 95% CIs and the

differences of these estimates between the darolutamide group and the placebo group will be presented. The SAS code will be similar to the following:

PROC LIFETEST DATA = <DATASET>;

*TIME EFFVAL * CENSORNY;*

STRATA TREATMGR;

RUN;

Description of rPFS events will be provided, i.e., the number of participants with progressive disease in soft tissue metastases or in bone metastases, and the number of deaths.

4.2.3 Sensitivity Analyses

The following sensitivity analyses will be performed for rPFS:

- Sensitivity analysis 1: considering the impact of all deaths at any time prior to data cutoff. All deaths from any cause at any time prior to data cutoff date, regardless the censoring rules, will be included in the rPFS calculation, unless rPD is documented.
- Sensitivity analysis 2: analysis with rPFS based on by investigator radiological assessment. Participants with a baseline superscan based on investigator review will be censored at date of randomization.
- Sensitivity analysis 3: analysis without stratification: using an un-stratified log-rank test and unstratified Cox model.
- Sensitivity analysis 4: analysis - considering the additional primary malignancy (except basal cell carcinoma) diagnosed prior to radiological progression or death, which will be censored at the date of last adequate tumor assessment before or on the diagnosis of additional primary malignancy.
- Sensitivity analysis 5: analysis without considering the censoring rule of radiological progression / death occurring later than (24+1) weeks of last adequate scan.
- Sensitivity analysis 6: considering the impact of rPD by central review documented between the scheduled scans as per protocol (every 12 weeks) the following will be implemented:
    1. For the tumor assessment within the scheduled visit time interval (every 12 +/- 1 weeks from randomization), the actual tumor assessment date will be used for rPFS;
    2. For the tumor assessment outside the scheduled visit time interval (i.e. outside of the every 12 +/- 1 weeks from randomization period): tumor assessment date of rPD will be moved forward to the date of next scheduled visit; tumor assessment date of non-rPD will be moved backward to the closest prior scheduled visit.
    3. rPFS will be the time from randomization to rPD or death or withdrawn informed consent or data cutoff, whichever comes first.
    4. This sensitivity analysis will not consider the censoring rules of radiological progression / death occurring later than (24+1) weeks of last adequate scan, and subsequent anticancer therapy starting prior or without radiological progression or death.

4.3 Secondary Endpoints Analysis

If the primary endpoint rPFS is significant, secondary efficacy endpoints will be tested with the hierarchical gatekeeping procedure. The order of secondary endpoints is as follows:

- Overall survival (OS)
- Time to initiation of subsequent anti-cancer therapy
- Time to castration-resistant prostate cancer (CRPC)
- Time to PSA progression
- PSA undetectable rates
- Time to pain progression

Safety endpoint:

- AE assessments using NCI CTCAE (v.5.0)

4.3.1 Overall Survival

Overall survival (OS) is defined as the time from the date of randomization to the date of death from any cause. OS is calculated as 'the date of death due to any cause – date of randomization'. Participants who are alive at the time of analysis will be censored according to the censoring rules specified in Table 4–2:

Table 4–2 Censoring rules for OS

Situation	End Date	Censored
Death during study	Death date	No
No death with no contacts after randomization	Date of randomization	Yes
No death	Last known alive date (LKAD) or database cut-off date, whichever comes earlier	Yes

Last Known Alive Date

The LKAD is derived from the main data sources. The last available date across all selected data panels listed below will be picked as the LKAD by participant. Information from selected data, i.e., visit dates, exposure information, laboratory measurements, tumor assessment dates, SSE dates, demographics, survival status date, vital signs and disposition events or follow-up assessments will be used to determine survival status. Within all the dates from the selected data panels, identify the latest available date as the LKAD for each participant.

For each formal analysis of OS a survival sweep starting immediately after the database cutoff date will be performed. The collected survival status will be included in the LKAD variable.

If a participant died and the date of death is completely or partially missing, but there is an AE with the outcome as 'Death', the date of death will be replaced by the end date of the AE. If there is such case, a sensitivity analysis will be performed without replacing the date of death by the end date of the AE.

If the complete date of death is not known, but the year and month are available and there is no AE with outcome as 'Death', Day 15 of the month will be used for the calculation of the time to death.

In rare circumstances of missing month and day of death, day 1 of the year (01Jan) will be used to compare with LKAD, the later date will be used for the date of death. Complete missing death date will not be imputed, the death with complete missing date will not be considered as a death event in any analysis.

The final OS analysis will occur when approximately 180 OS events have been observed. OS data as calculated above will be used for the primary analyses of OS at the interim and final OS analyses.

Once the primary completion study results are available, and if they support a positive benefit/risk assessment for darolutamide in the study by judgment of the Sponsor (considering feedback from the study steering committee and/or health authorities), those patients who are on study treatment (darolutamide or placebo) will be offered the opportunity to receive darolutamide through open-label treatment in this study. This may dilute the effect size for the OS endpoint as the placebo arm outcomes may become more similar to the darolutamide arm outcomes at the final OS analysis.

The amount of this bias can be approximately assessed by established crossover adjustment methods like Rank-Preserving Structural Failure Time (RPSFT) [3] or Iterative Parametric Estimation (IPE) [4]. These methods construct a placebo arm Kaplan-Meier curve which is expected to resemble the Kaplan-Meier (KM) curve which would be observed if placebo to darolutamide crossover would not have occurred. As a supportive analysis, the data of the final analysis of OS will be analyzed in addition with the RPSFT and IPE methods.

4.3.2 Time to castration-resistant prostate cancer

Time to castration-resistant prostate cancer (CRPC) is defined as the time from the date of randomization to the date of occurrence of the following events, whatever comes first:

- PSA progression with serum testosterone being at castrate level <0.50 ng/mL, is defined as a ≥25% increase above the nadir (lowest at or after baseline) value and an increase in absolute value of ≥2 ng/mL above nadir, and is at least 12 weeks from randomization date, which is confirmed by a second value 3 or more weeks later. All PSA values between the initial assessment meeting the PSA progression criteria and confirmation assessment must be ≥2 ng/mL and ≥25% increase above nadir, serum testosterone at castrate levels <0.50 ng/mL is requested at initial assessment.
- Radiological progression by malignant soft tissue lesions, which is determined by the central review based on Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 (1).
- Radiological progression by bone lesions, which is determined according to PCWG3 criteria (2) based on whole body ^{99m}Tc methylene diphosphonate bone scans assessed by the central review.
- Occurrence of symptomatic skeletal event (SSE).

The following censoring rules in Table 4–3 will be applied:

Table 4–3 Censoring rules for time to CRPC

Situation	End Date	Censored
Castration-resistant prostate cancer (CRPC) event	The earliest event date among the four components	No
No baseline assessment for CRPC relevant assessments (PSA assessments and radiological assessments)	Date of randomization	Yes
No post-baseline assessment for CRPC relevant assessments	Date of randomization	Yes
CRPC occurs later than (24+1) weeks of last CRPC relevant assessments (PSA assessments and radiological assessments)	Date of the last CRPC relevant assessment before the consecutive missing assessments	Yes
No CRPC event	Date of last CRPC relevant assessment or randomization date (censored at Day 1 if there is no follow-up available), whichever is later	Yes
Subsequent anticancer therapy before CRPC event	Date of last CRPC relevant assessment before or on subsequent anticancer therapy start date or randomization date, whichever comes later	Yes

A summary of first CRPC events will be provided. Participants with multiple events are only counted for the category in which the first event occurred. If multiple CRPC events (component events) occur on the same date for one participant, the participant is only counted into one category in the order of: SSE > radiological soft tissue/ visceral lesion progression > radiological bone progression > PSA progression.

The primary analysis of time to CRPC will be based on central PSA assessments only.

A sensitivity analysis of time to CRPC will be performed without considering the occurrence of SSE as a CRPC event. The censoring rules of this sensitivity analysis will be the same as the censoring rules for the primary analysis of time to CRPC except excluding SSE assessments.

4.3.3 Time to initiation of subsequent anticancer therapy

Time to initiation of subsequent anticancer therapy is defined as the time from the date of randomization to the date of initiation of first subsequent anti-cancer therapy for prostate cancer. The systemic anticancer therapy is defined in appendix 8.3.

The following censoring rules in Table 4–4 will be applied:

Table 4–4 Censoring rules for time to initiation of subsequent anticancer therapy

Situation	End Date	Censored
Initiation of first subsequent anticancer therapy for prostate cancer	Start date of first subsequent anti-cancer therapy for prostate cancer	No
No subsequent anticancer therapy for prostate cancer	Date of last visit, or randomization date, whichever comes later	Yes

A summary of first subsequent anticancer therapy for prostate cancer will be provided.

4.3.4 Time to PSA progression

Time to PSA progression, is defined as the time from the date of randomization to the date of first PSA progression. Participants without PSA progression as of database cut-off, whether or not surviving, will be censored at the last total PSA laboratory assessment date as detailed in Table 4–5.

PSA progression with serum testosterone being at castrate level <0.50 ng/mL, is defined as a ≥25% increase above the nadir (lowest at or after baseline) value and an increase in absolute value of ≥2 ng/mL above nadir, and is at least 12 weeks from randomization date, which is confirmed by a second value 3 or more weeks later. All PSA values between the initial assessment meeting the PSA progression criteria and confirmation assessment must be ≥2 ng/mL and ≥25% increase above nadir, serum testosterone at castrate levels <0.50 ng/mL is requested at initial assessment.

Table 4–5 Censoring rules for time to PSA progression

Situation	End Date	Censored
PSA progression during study	Event assessment date	No
No baseline PSA assessment	Date of randomization	Yes
No post-baseline PSA assessment	Date of randomization	Yes
No PSA progression	Date of last PSA assessment or randomization date, whichever is later	Yes
PSA progression event occurs later than (24+1) weeks of last PSA assessments	Date of the last PSA assessment before the consecutive missing ones	Yes

The analysis of PSA progression will be based on central PSA assessments from baseline to EOT visit.

4.3.5 PSA undetectable rate

PSA undetectable rate is defined as the percentage of participants with detectable PSA values of ≥0.2 ng/mL at baseline which become undetectable with any PSA values <0.2 ng/mL during the period between randomization and 30 days after last dose of study drug or start of new anti-cancer therapy whichever occurred earliest, based on the participants had detectable

PSA value at baseline The analysis of PSA undetectable rate will be based on central PSA assessments.

4.3.6 Time to pain progression

Time to pain progression is defined as the time from the date of randomization to the date of first pain progression. Pain progression will be assessed by Question 3 (Q3) of the BPI–SF questionnaire (Appendix 8.48.3) related to the worst pain in the last 24 hours (worst pain subscale [WPS]) taken as an average for post baseline score, or initiation of short or long-acting opioids for malignant disease for ⩾7 consecutive days after randomization. Initiation or change in the use of other non-opioid analgesics is not used in the assessment of pain progression.

WPS score is taken as an average score of Q3 of the BPI-SF questionnaires answered within 7 days prior to each reporting timepoint. If there are more than 7 daily questionnaires answered at a reporting time point, then the latest 7 questionnaires to reporting timepoint will be used to assess the pain progression.

The pain progression is defined as:

- For asymptomatic participants with WPS=0 at baseline, pain progression is defined as an increase of 2 or more points in the WPS score from nadir (i.e., zero) observed at 2 consecutive evaluations ≥4 weeks apart, or initiation of short- or long-acting opioid use for malignant disease for ⩾7 consecutive days after randomization.
- For symptomatic participants with WPS >0 at baseline, pain progression is defined as an increase of 2 or more points in the WPS score from nadir observed at 2 consecutive evaluations ≥4 weeks apart and a WPS ≥5, or initiation of short- or long-acting opioid use for malignant disease for ≥7 consecutive days after randomization.

Time to pain progression will be calculated as the ‘the earliest date of 7-day Q3 questions answered, or initiation of short- or long-acting opioid use for malignant disease for ≥7 consecutive days, whichever comes first, minus randomization date’.

The following censoring rules in Table 4–6 will be applied:

Table 4–6 Censoring rules for time to pain progression

Situation	End Date	Censored
Pain progression during study	Start date of first pain progression	No
No WPS baseline pain assessment	Date of randomization	Yes
No WPS post-baseline pain assessment and no post-baseline opioid use for malignant disease for ≥7 consecutive days	Date of randomization	Yes
Death during the study before pain progression	Date of last valid pain progression assessment or randomization date, whatever comes later	Yes

No pain progression	Date of last valid pain progression assessment or randomization date, whatever comes later	Yes

Sensitivity analyses of time to pain progression will be performed by considering a minimum number of 2, 3, and 4 daily reports (i.e., Q3 question must be answered) answered within 7 days prior to each reporting time point as a valid pain progression assessment. The censoring rules in Table 4–6 will be applied for the sensitivity analyses.

4.3.7 AE assessments

Frequency and severity of AEs per CTCAE v. 5.0 are considered as secondary endpoints.

AEs will be reported in the CRF in terms of their seriousness, intensity (severity) according to NCI-CTCAE, v. 5.0, and relationship to the study drugs. Refer to Section 4.5.2 for the details of the analyses.

4.3.8 Main Analytical Approach

The secondary estimand is prescribed in Section 1.1. All secondary efficacy endpoints will be analyzed in the FAS population. Time-to-event endpoints will be analyzed with the same methods as described for the primary endpoint rPFS.

Descriptive statistics of survival follow-up time will be calculated by treatment arm and total. Survival follow-up time is the time to LKAD or death as described for the OS endpoint for censored and uncensored participants.

PSA undetectable rate will be compared between treatment arms using Cochran-Mantel-Haenszel test adjusting for same stratification factors as used for randomization. Estimates and the 95% CI will be computed for each treatment arm.

Sample code for Cochran-Mantel-Haenszel test:

PROC FREQ DATA=DATASET;

*TABLES_STRATA_1*STRATA_2*PSA_UNDETECTABLE*TREATMGR /CMH;*

RUN;

Where:

PSA_UNDETECTABLE contains PSA undetectable values, *TREATMGR* contains assigned treatment arm, *STRATA_1 and STRATA_2 are the stratification variable values* at randomization.

The analyses of AEs are described in Section 4.5.2.

4.4 Other Pre-Specified Endpoints

Other pre-specified endpoints are:

- Progression-free survival 2 (PFS2) as assessed by the investigator
- Time to symptomatic skeletal event (SSE)
- Alterations of markers related to prostate cancer and androgen receptor inhibition such as androgen receptor (AR) alterations, alternative AR splice variants (e.g., AR V7), PTEN loss. (For China, only AR gene alterations, AR V7 splice variants and PTEN loss are applicable).

- Time to deterioration in the Functional Assessment of Cancer Therapy – Prostate Cancer (FACT-P) total score
- Time to first prostate cancer-related invasive procedure

4.4.1 Progression-free survival 2 (PFS2)

Progression-free survival 2 (PFS2) assessed by the investigator is defined as the time from the date of randomization to the date of first occurrence of clinical, biochemical, or radiological disease progression under first subsequent anticancer therapy (ACT) for prostate cancer or death, whichever occurs first.

Participants who have no disease progression or death during the first subsequent ACT for prostate cancer and participants who do not receive first subsequent ACT for prostate cancer will be censored according to the censoring rules specified in Table 4–7.

Table 4–7 Censoring rules for PFS2 based on investigator assessment

Situation	End Date on or prior to cut-off date	Censored
Documented disease progression during 1st subsequent ACT for prostate cancer	Date of documented progression after starting 1st subsequent ACT for prostate cancer	No
Not received any subsequent ACT for prostate cancer (either still receiving study treatment without disease progression or discontinued study treatment but did not start any subsequent ACT or received subsequent ACT for additional primary malignancy)	Last adequate tumor assessment date under study treatment per investigator assessment or randomization date, whichever is later	Yes
No documented progression during 1st subsequent ACT for prostate cancer or death	The end date of the first subsequent ACT for prostate cancer; If first subsequent ACT for prostate cancer is on-going: the date of LKAD for the participants discontinuced study or lost follow up, otherwise on data cutoff date	Yes
Documented baseline superscan based on investigator review	Date of randomization.	Yes

4.4.2 Time to symptomatic skeletal event

Time to symptomatic skeletal event (SSE) is defined as the time from the date of randomization to the date of first occurrence of SSE. An SSE is defined as EBRT to relieve skeletal symptoms, or new symptomatic pathologic bone fracture, or occurrence of spinal cord compression or tumor–related orthopedic surgical intervention, whichever comes first. The censoring rules in Table 4–8 will be applied.

Table 4–8 Censoring rules for time to first SSE

Situation	End Date	Censored
SSE during study	Date of the first assessment with SSE event	No
No SSE	Randomization date or date of last SSE assessment (i.e. last visit up to active follow up), whichever comes later	Yes

A summary of first SSE will be provided. Participants with multiple events are only counted for the category in which the first event occurred. If multiple SSEs (component events) occur on the same date for one participant, the participant is only counted into one category in the order of: spinal cord compression > bone fracture > orthopedic surgery > EBRT.

4.4.3 Biomarkers

Biomarker analyses will be described in a separate biomarker analysis plan. Results from exploratory biomarker analyses will be reported in a separate biomarker report.

4.4.4 Time to deterioration in FACT-P total score

Deterioration for the FACT-P total score is defined as a 10-point or more decline from baseline in the total score.

A participant's time to deterioration is defined as the time from randomization to the deterioration date. For participants with no symptomatic deterioration at the time of the analysis, the time to deterioration will be censored according to the censoring rule specified in Table 4–9. For participants with missing baseline FACT-P total score time to deterioration will not be calculated.

Table 4–9 Censoring rules for time to deterioration in the Functional Assessment of Cancer Therapy-Prostate Cancer (FACT-P) total score

Situation	End Date	Censored
Deterioration in the functional assessment of FACT-P total score	Start date of deterioration in the functional assessment of FACT-P total score	No
No deterioration in the functional assessment of FACT-P total score	Date of last functional assessment of FACT-P total score, or randomization date, whichever comes later	Yes
No baseline or post baseline functional assessment of FACT-P total score	Date of randomization	Yes

4.4.5 Time to first prostate cancer-related invasive procedure

Time to first prostate cancer-related invasive procedure is defined as time from the date of randomization to the date of first prostate cancer-related invasive procedure. Prostate cancer-related invasive procedure is defined as any procedure needed for alleviation of symptoms, signs or findings caused by progression of prostate cancer (e.g., catheterization of the bladder, percutaneous drainage of hydronephrosis, palliative electro resection of the prostate, etc.). Status of cancer-related invasive procedure will be assessed from randomization until the first cancer-related invasive procedure or change of anti-cancer therapy, whatever occurs first.

Participants who have no prostate cancer-related invasive procedure will be censored according to the censoring rules specified in Table 4-10.

Table 4–10 Censoring rules for time to first prostate cancer-related invasive procedure

Situation	End Date	Censored
Prostate cancer-related invasive procedure	The date of first prostate cancer-related invasive procedure	No
No prostate cancer-related invasive procedure	Date of last assessment for invasive procedure, or randomization date, whichever comes later	Yes

4.4.6 Main Analytical Approach

All other pre-specified efficacy endpoints will be analyzed in the FAS population. Time-to-event endpoints will be analyzed with the same methods as described for the primary endpoint rPFS.

4.5 Safety Analyses

4.5.1 Extent of Exposure

As a general rule, trailing "0 mg" records, which are not followed by any positive amount of drug will not be included in the calculation of any drug duration or amount. Similarly, the according trailing "drug interruptions" will not be used in statistical tables. A footnote will be included, stating that "Interruption becoming permanent study treatment discontinuation is not accounted as an interruption".

Descriptive statistical summaries will be provided by treatment arm in SAF population for the following variables:

- Overall time under treatment [months]: will be calculated in days and presented in months as (date of the last dose of any study treatment – date of the first dose of any study treatment + 1) / 30.44. It includes time off drug and dose interruptions.
- Actual time under treatment [months]: will be calculated in days and presented in months as (date of the last dose of any study treatment – date of the first dose of any study treatment + 1) / 30.44. It excludes time off drug and dose interruptions.
- Actual dose per day [mg/day]: will be calculated as (total amount of dose / number of days with intake > 0)
- Total amount of dose [mg]: will be calculated as (sum of dose received over total time under treatment)
- Percent of planned dose received [%]: will be calculated as (total amount of dose [mg] / planned dose [mg] * 100%); planned dose is sum of the intended initial dose according to protocol over total time under treatment.

For the participants on treatment at the time of data cutoff, the cutoff date will be used in the calculation of time under treatment.

For participants with dose reduction, re-escalations, interruption; the number of dose reductions, re-escalations, interruptions, per participant and their reasons will be summarized.

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

4.5.2 Adverse Events

AEs will be coded using MedDRA 25.0 or the most recent version. The severity (or intensity) of AEs will be documented using the National Cancer Institute-Common Terminology Criteria for Adverse Event (NCI-CTCAE) v. 5.0). Descriptive summary tables will be presented on all safety parameters by treatment arm.

The AEs will be presented with their worst NCI-CTCAE v. 5.0 grade. AEs will be classified by the investigator as related or not related to study drug (darolutamide or placebo).

Treatment-emergent AE (TEAE) is defined as any event arising or worsening after the first dose of study drug until 30 days after the last dose of study drug.

Summary statistics (frequency and percentage of participants, not of events) will be presented by treatment arm, MedDRA SOC and PT, and NCI-CTCAE worst grade for the following:

- Incidence of all TEAEs
- Incidence of TEAEs for NCI-CTCAE Grade 3, 4 or 5
- Incidence of TEAEs with incidence of ≥5%
- Incidence of TEAEs leading to permanent discontinuation of treatment
- Incidence of TEAEs leading to dose reduction
- Incidence of TEAEs leading to dose interruption
- Incidence of all study drug-related TEAEs
- Incidence of study drug-related TEAEs for NCI-CTCAE Grade 3, 4 or 5
- Incidence of study drug-related TEAEs with incidence of ≥5%
- Incidence of study drug-related TEAEs leading to permanent discontinuation of treatment
- Incidence of study drug-related TEAEs leading to dose reduction
- Incidence of study drug-related TEAEs leading to dose interruption
- Incidence of pre-treatment AEs and post-treatment AEs (after 30 days from the last dose of study drug)
- Incidence of COVID-19 pandemic related TEAEs

In addition, a listing of TEAEs leading to permanent discontinuation of treatment and a listing of all AEs will be provided.

Deaths and serious adverse events

Treatment-emergent serious adverse events (TESAEs) will be summarized by treatment arm, MedDRA SOC/PT and by NCI CTCAE worst grade for the following:

- Incidence of TESAEs
- Incidence of TESAEs leading to permanent discontinuation of study treatment

- Incidence of TESAEs leading to dose reduction
- Incidence of TESAEs leading to drug interruption
- Incidence of study drug-related TESAEs
- Incidence of COVID-19 pandemic related TESAEs

In addition, listings of TESAEs and non-treatment-emergent SAEs will be provided.

The incidence of deaths in the study within 30 days after first dose of study drug, during study treatment from first to last dose of study drug, within 30 days after last dose of study drug, later than 30 days after last dose of study drug, will be summarized by each treatment arm and cause of death. All deaths before treatment start, during treatment and within 30 days after last dose of study drug, and later than 30 days after last dose of study drug, will be listed by participant with start and stop date of study medication, date of death, and cause of death.

Exposure-adjusted incidence rates

To adjust for unequal lengths of study treatment between the treatment arms, additional analyses based on exposure time will be performed for all TEAEs, special topics TEAEs, and all TESAEs occurring after the first dose of darolutamide or placebo. The exposure-adjusted incidence rate is calculated as the total number of participants with a given TEAE divided by the sum of exposure time in years. For a participant with at least one TEAE, the exposure time is the time from first treatment to first TEAE; for a participant without TEAE, the exposure time is the sum of treatment duration and time at risk after treatment end, where time at risk after treatment end is the time after end of treatment to the earliest date of death, data cut-off, end of treatment-emergent window, or lost follow-up , or withdrawal from study. The rate is expressed in 100 participant years.

The exposure time in years will be calculated as treatment duration in days divided by 365.25. The risk difference and risk ratio will be calculated together with 95% confidence intervals (CIs). No zero-cell correction will be applied for calculation of the risk ratio, i.e., in case of no events in the placebo arm the risk ratio will not be calculated. The incidence rate ratio for darolutamide arm vs. placebo arm will also be calculated.

Adverse Events of Special Interest

No AEs of special safety interest were defined in this study.

Special Topic of Adverse Events

The following TEAE groupings are considered as special topics (see definitions in Appendix 8.6):

- Bone fractures excluding pathological fractures
- Diabetes mellitus and hyperglycemia
- Fall
- Fatigue/ asthenic conditions
- Weight decreased
- Rash
- Seizure

- Hypertension
- Vasodilatation and flushing
- Mental impairment disorders
- Depressed mood disorders
- Breast disorders/gynecomastia
- Cardiac disorders
- Cerebral ischaemia
- Cerebral and intracranial hemorrhage
- Interstitial lung disease

The following tables will be created for TEAEs of special topics:

- Incidence of TEAEs
- Incidence of TEAEs leading to permanent discontinuation of study treatment
- Incidence of TEAEs leading to dose reduction
- Incidence of TEAEs leading to dose interruption
- Incidence of TESAEs

The following analyses will be performed with incidence of greater than least 5%. Bone fracture events (excluding pathological fractures) will be described by a cumulative incidence plot of fracture obtained using the Aalen-Johansen estimator. Timing of occurrence of bone fracture events based on first dose of study drug will be presented. A summary of time to the first bone fracture and the first fall event will be presented in descriptive and inferential statistics, respectively. In addition, cumulative incidence plots will be created to display the time to the first fall and time to the first bone fracture. Treatment discontinuation and death will be considered risks competing with the occurrence of fractures.

A summary of treatment-emergent fracture by bone health agent use (for selection of bone health agent see Appendix 8.7) at study entry will be provided.

A listing of participants with fracture events breakdown by relevant events occurring within 7 days window: fall, accident, syncope and/or loss of consciousness, dizziness will be presented.

A listing will be generated for participants with fall treatment-emergent events with syncope and/or loss of consciousness (using the MLG Syncope).

A listing of participants with MLG seizure as medical history and a listing of participants developing MLG seizure as adverse event will be presented.

Additional Primary Malignancies

Summary statistics (frequency and percentage of participants, not of events) will be presented by treatment arm, MedDRA SOC and PT for additional primary malignancies. A listing will be generated for participants with additional primary malignancies.

The additional primary malignancies are defined by: SMQ Malignant tumors, excluding: the following terms:

- PT: Hormone-dependent prostate cancer
- PT: Hormone-refractory prostate cancer
- PT: Prostate cancer
- PT: Prostate cancer metastatic
- PT: Prostate cancer recurrent
- PT: Prostate cancer stage 0
- PT: Prostate cancer stage I
- PT: Prostate cancer stage II
- PT: Prostate cancer stage III
- PT: Prostate cancer stage IV
- PT: Cancer in remission
- PT: Neuroendocrine carcinoma of prostate
- PT: Neuroendocrine cancer of the prostate metastatic
- PTs from HLGT: Metastases
- LLT: Progression of pre-existing cancer

4.5.3 Additional Safety Assessments

4.5.3.1 Laboratory safety assessments

The following laboratory parameters will be summarized:

- Hematology panel: hematocrit, hemoglobin, red blood cell (RBC) count including mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), %Reticulocytes, white blood cell (WBC) count, platelet count, and differential blood count reported as absolute count or percentage for neutrophils, lymphocytes, monocytes, eosinophils, and basophils
- Chemistry panel, including bold urea nitrogen (BUN), serum creatinine, sodium, potassium, calcium, total and direct bilirubin, total ALP, AST, ALT, SGPT, SGOT, albumin, total protein, and glucose
- Urinalysis: specific gravity, pH, glucose, protein blood, ketones
- Other parameters: PSA, serum testosterone.

Descriptive statistics (number of observations, mean, standard deviation, minimum, median and maximum values) will be presented for clinical laboratory tests (hematology, clinical biochemistry and urinalysis), their changes from baseline (including baseline value) at applicable visits.

For laboratory parameters with numeric values that do not overlap between grades based on CTCAE V 5.0, the following table will be created:

- Laboratory abnormalities worsening from baseline.

For laboratory parameters where numeric values overlap between grades or with no numeric value available, the grading is differentiated through signs, symptoms or therapies based on CTCAE V 5.0, the following shift table will be created:

- Worst laboratory value during intervention period by baseline category.

For laboratory parameters without any numeric values in CTCAE V 5.0 - Hyperglycemia, following table will be created based on CTCAE V 4.03:

- Laboratory abnormalities worsening from baseline.

Clinical laboratory toxicities collected after the start of first dose up to 30 days after the last dose of darolutamide/placebo will be considered as “treatment-emergent".

The last non-missing value before or (without timing of information) on the first day of study drug will be retained as “baseline” data. If the “baseline” data have several assessments the average of the values will be considered as “baseline” value.

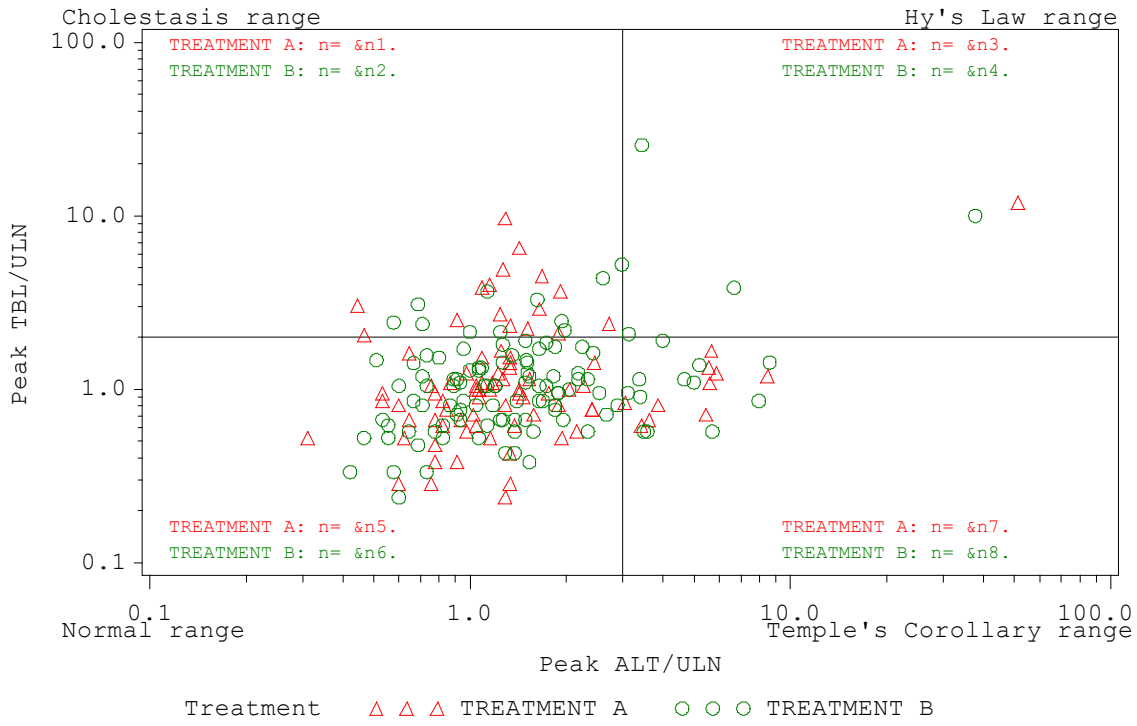
The laboratory values will also be categorized into low, normal and high according to their reference ranges.

Descriptive statistics will be calculated by treatment arm and visit.

The data will also be displayed graphically using box plots and laboratory shift plots. These will show the baseline value and post baselines values up-to end of treatment.

A listing will be provided for all participants possibly fulfilling Hy’s Law criteria, i.e., participants with elevated AST and / or ALT ≥ 3xULN, alkaline phosphatase < 2xULN and bilirubin > 2xULN. For possible Hy’s Law cases relevant laboratory data will also be displayed graphically within actual participant profiles (presenting total bilirubin, ALT, AST and ALP values in terms of ULN over time) by treatment arm. Below example of Hy’s law plot will be provided for peak total bilirubin vs ALT. If a participant has any total bilirubin > 2xULN then peak bilirubin will be plotted versus the maximum ALT amongst the total bilirubin > 2xULN. Otherwise, peak bilirubin will be plotted versus peak ALT.

Figure 4–1 Example for Hy's law plot



Unscheduled laboratory data will not be included in the by-visit summary tables but listed in Section 10 of the CSR.

4.5.3.2 Analyses of drug-induced liver injuries

Analyses of potential drug-induced liver injuries:
Treatment emergent laboratory test values collected after the start of first dose up to 30 days after the last dose of darolutamide/placebo will be used to analyze any potential drug-induced liver injury (DILI) case. In participants who meet the criteria of a potential DILI, below listing/plot will be provided:

- Individual listing including visit date, study day, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), alkaline phosphatase (ALP), direct bilirubin and creatinine kinase,

In addition, the following summary will be provided for participants with at least one measurement in SAF:

- Incidence and exposure-adjusted incidence rate (EAIR) of the worst treatment-emergent hepatic laboratory value will be provided by the following laboratory parameters with category:
  - ALT: ≥ 1×ULN, ≥3×ULN, ≥ 5×ULN, ≥ 8×ULN, ≥ 10×ULN, ≥ 20×ULN
  - AST: ≥ 1×ULN, ≥3×ULN, ≥ 5×ULN, ≥ 8×ULN, ≥ 10×ULN, ≥ 20×ULN
  - ALP: ≥ 1.5×ULN, ≥2×ULN, ≥3×ULN
  - Total Bilirubin: ≥ 2×ULN, ≥5×ULN, ≥8×ULN

Incidence and EAIR will be provided for TEAE, TEAE leading to permanent discontinuation of treatment, TESAE with Standardized MedDRA Queries (SMQ) 'Drug related hepatic disorders - comprehensive search'.
The EAIR definition refers to Section 4.5.2.

4.5.3.3 Other Safety Measures

12-lead ECG

Analyses of ECG and QTc will be performed in the SAF population; no subgroup tables will be created.

Descriptive statistics including arithmetic mean, SD, median, minimum, and maximum will be presented for the following ECG parameters: QT, QTcB (derived) and QTcF (derived). Parameters will be summarized for actual results and the change from baseline for the safety analysis set by treatment arm at each scheduled visit. Baseline for 12-lead ECG will be the mean of separate recordings. Similarly, post baseline values of 12-lead ECG will be the mean of separate recordings.

Mean time courses +/- one standard deviation will be displayed graphically.

The last non-missing value before the first study drug intake will be considered as “baseline” data.

If several assessments are performed on the same day (without timing information) the average of the values will be considered.

In case ECG is missing at day 1 then the screening assessment will be considered as baseline data.

The number and percent of participants with absolute QTc interval prolongation or QTc increase from baseline will be defined and summarized by treatment arms.

The number of participants with QTC interval (max value) ≤ 450 msec, > 450-480 msec, > 480-500 msec and > 500 msec data will also be displayed graphically using a bar chart.

Unscheduled ECG data will be listed (in Section 10 of the CSR) but will not be displayed in the by-visit summary tables.

Vital signs

For each treatment arm, vital signs (i.e., blood pressure, heart rate, and weight) will be tabulated and summarized by visit for observed values and changes from baseline using descriptive statistics, as appropriate. If more than one baseline assessment is collected, the most recent one will be used. If several assessments are performed on the same day (without timing information) the average of the values will be considered.

In addition to descriptive analysis box plots will be created.

For weight parameter a graph representing mean changes in weight from baseline by visit will be created.

The number and percentage of patients with outlying values will be tabulated by treatment arm.

Unscheduled vital signs data will be listed (Section 10 of the CSR) but will not be displayed in the by-visit summary tables.

4.6 Other Analyses

4.6.1 Other Variables and/or Parameters

4.6.1.1 Patient Reported Outcome (PRO)

Patient Reported Outcome (PRO) data as measured by the FACT-P and BPI-SF will be analyzed to assess differences in health-related Quality of Life (HRQoL) and health utility values between treatment arms based on time-adjusted Area Under the Curve (AUC) using all available data. Quality of Life and PRO data analyses specified in this section are based on - electronic patient-reported outcome (ePRO) device, or paper forms.

The FACT-P questionnaire assesses prostate cancer-related quality of life and has been validated in the prostate cancer population. This questionnaire contains 5 subscales: Physical Well-Being (PWB), Social/Family Well- Being (SWB), Emotional Well-Being (EWB), Functional Well-Being (FWB), and Additional Concerns (also called Prostate cancer subscale [PCS]).

According to the FACT-P scoring guide, all subscale items are summed to a total which is the subscale score. Subscale score will be calculated by multiplying the sum of the individual item scores by the number of items in the subscale, then dividing the number of items answered, if more than 50% items of this subscale is answered. Otherwise, the subscale score will be missing. FACT-P total score is calculated as the sum of five subscale scores (PWB, SWB, EWB, FWB and PCS), if all of five subscales have a valid value and more than 80% of all items answered. The details of FACT-P scoring are provided in Appendix 8.5. The higher the score, the better the quality of life of prostate cancer participants.

The BPI-SF is completed daily over a 7-day period. Averages of each question during the period of reporting are calculated.

Two scores will be derived from BPI-SF: the pain severity and the pain interference.

The BPI assesses pain at its “worst” “least” “average” and “right now” (current pain). To derive the “pain severity” score, a mean score of the average of 4 questions (questions 3 to 6 from the BPI-SF) over 7-day period related to pain will be created, given all 4 questions have valid score over 7-day period.

The pain interference is scored as the mean of the average of 9 questions scores (question 9A-9G in the BPI-SF) over 7-day period, given that more than 50% (i.e., minimum 4 questions out of 7), of the questions have valid score over 7-day period.

The PRO analyses will be performed for the participants in the FAS. Statistical tests will be performed with a one-sided test with type I error 0.025 (equivalent a two-sided test with type I error 0.05). The p-values are for descriptive purposes only.

Descriptive statistics on observed data will be presented for FACT-P questionnaire (each domain score including the PCS and the FACT-P total score) and for BPI-SF questionnaire (pain severity and pain interference scores) at each assessment time point and for change from baseline by treatment arm. Figures of FACT-P total score, pain severity and pain interference scores at each assessment time point during the treatment period and follow-up period will be provided. Questionnaires under unscheduled visits and not planned visits per protocol will not be displayed in the descriptive tables. Analyses will be done for participants with baseline assessments.

Listings of FACT-P trial outcome index (TOI) and FACT-G total score in addition to FACT-P total score, pain severity and pain interference scores will be provided. The calculation of FACT-P TOI and total score are provided in Appendix 8.5, those two scores will be calculated if all specified subscales have a valid value and more than 80% of all items answered, respectively.

The frequency for missing health related quality of life (HRQoL) assessment by treatment arm will be summarized.

An analysis of covariance (ANCOVA) model (a mixed linear model, with random coefficient) and with covariates for baseline PRO scores and stratification factors as recorded in the IWRS data for FACT-P total and subscale scores, BPI-SF pain severity or interference scores in the time-adjusted Area under Curve (AUC) will be used to estimate the mean difference and treatment effect between the two treatment arms. Least-square mean estimates, standard errors and 95% CIs will be estimated for each treatment arm and for the treatment arm difference.

Calculation of Time-adjusted AUC:

AUC will not be calculated if baseline data is missing.

The trapezoidal rule will be used to derive the AUC for a participant for the FACT-P total and subscale scores, BPI-SF pain severity and interference scores. The time-adjusted AUC will be calculated by dividing the AUC by the duration (in days) over the treatment period. When calculating the AUC, the exact date of completion of the questionnaires should be plotted and the duration will be calculated in days. The time adjusted AUC for the FACT-P subscale scores and total score, BPI-SF pain severity and interference scores for an individual participant over a period of time [Ta,Tb] will be calculated as follows:

$$AUC_{a\text{-}b} = \frac{1}{2(T_b - T_a)} \sum_{i=a}^{b-1} (PRO_i + PRO_{i+1})(T_{i+1} - T_i)$$

Where PRO_i is the PRO measurement at time T_i (i=a… b). For the AUC of BPI-SF pain severity and interference scores, T_i is the earliest date of 7-day valid BPI-SF form completed.

4.6.1.2 ECOG PS

ECOG PS will be summarized with descriptive statistics and frequency tables. Changes from baseline to worst post-baseline ECOG PS score during treatment will be summarized in shift tables by treatment arm. In addition, changes from worst post-baseline ECOG PS score during treatment to EOT score will be summarized in a shift table by treatment arm.

4.6.2 Subgroup Analyses

4.6.2.1 Subgroup analyses of efficacy endpoints

Subgroup analyses will be conducted for the primary efficacy endpoint rPFS and secondary efficacy endpoint OS based on the FAS population, non-stratified Cox regression model and non-stratified log-rank test will be used. Descriptive statistics and HR estimates with 95% CI will be provided at least for the subgroups listed below, provided there are a sufficient number of events in total within the subgroup across the treatment arms. Forest plots of the HRs will be generated.

- Presence of visceral metastases assessed by central review (Yes vs. No) (from IWRS)
- Received prior local therapy (Yes vs. No) (from IWRS)

- Prior local radiotherapy and/or prostatectomy (Yes, No) (selection provided in Appendix 8.10)
- Age group (<65, 65–74, 75–84 and ≥85 years)
- Race (White, Asian, Black or African American, Other)
- Geographical region
    - Asia (China, India, Taiwan)
    - Latin America (Brazil, Chile, Peru)
    - Europe and Rest of the world (Australia, Canada, Spain, Lithuania, Latvia, New Zealand, Russia, Ukraine, and South Africa)
- Baseline PSA values by median (< median of overall population, ≥ median of overall population)
- ECOG PS at baseline (=0, ≥1)
- Gleason score at initial diagnosis (Gleason <8, Gleason ≥8)
- Disease volume at baseline (high and low)

4.6.2.2 Subgroup analyses of TEAEs

The following subgroup analyses will be performed for overview of TEAEs, TESAEs, TEAEs with incidence of greater than least 5%, and for TEAEs showing at least 5% point differences in incidence proportions between any of the subgroup categories:

- Age category (<65, 65–74, 75–84, ≥85 years)
- Geographical region
    - Asia (China, India, Taiwan)
    - Latin America (Brazil, Chile, Peru)
    - Europe and Rest of the world (Australia, Canada, Spain, Lithuania, Latvia, New Zealand, Russia, Ukraine, and South Africa)
- Renal function – eGFR at baseline
    - Normal: eGFR ≥ 90 mL/min
    - Mild impairment: 60 ≤ eGFR < 90 mL/min
    - Moderate impairment: 30 ≤ eGFR < 60 mL/min
    - Severe impairment: 15 ≤ eGFR < 30 mL/min

  eGFR will be calculated according to the Modification of Diet in Renal Disease (MDRD) Formula:

  $$eGFR\ (mL/min/1.73m^2) = 186 \times SCR^{-1.154} \times age^{-0.203} \times (0.742, \text{if female}) \times (1.212 \text{ if blacks or African American}) \times (0.881 \text{ if Japanese}) \times (1.227 \text{ for Chinese (mainland China, Taiwan and Hongkong)})$$

  where SCR= serum creatinine measured in mg/dL
- Hepatic function at baseline
    - Normal: Total bilirubin and AST ≤ upper limit of normal (ULN)

- Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin ≤ ULN and AST > ULN)
- Moderate impairment: Total bilirubin > 1.5 to 3 x ULN, any AST
- Severe impairment: Total bilirubin > 3 x ULN, any AST.

- ECOG PS at baseline (0, ≥1)
- Medical history
  - Incidence of TEAEs (SOC/HLGT/HLT/PT and worst CTCAE grade) will be summarized by treatment arm for the following subgroups:
    - Participants with medical history of hepatic impairment (PT: Alcoholic liver disease, Cirrhosis alcoholic, Drug-induced liver injury, Endoscopic retrograde cholangiopancreatography, Hemangioma of liver, Hepatic cirrhosis, Hepatic function abnormal, Hepatic steatosis, Hepatitis, Hepatitis alcoholic, Hepatobiliary disease, Hepatomegaly, Liver abscess, Liver disorder, Liver transplant, Steatohepatitis) will be summarized by treatment arm.
    - Participants with medical history of renal impairment (SMQ Acute renal failure; SMQ Chronic kidney disease).
  - Incidence of TEAEs cardiac disorder (SOC/HLGT/HLT/PT and worst CTCAE grade) for subgroup of participants with medical history of cardiac disorder will be summarized by treatment arm.
  - Incidence of special topic TEAEs hypertension (MLG, PT and worst CTCAE grade) for subgroup of participants with medical history of MLG hypertension, PTs Hypertensive crisis, Hypertensive emergency will be summarized by treatment arm.

An overview of TEAEs according to specific categories per EMA guidance by age categories (<65, 65–74, 75–84 and >85) will be provided. The following selections will be used:

- Anticholinergic syndrome: SMQ ‘Anticholinergic syndrome’,
- Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures
- Psychiatric disorders (SOC)
- Nervous system disorders (SOC)
- Accidents and injuries (SMQ)
- Cardiac disorders (SOC)
- Vascular disorders (SOC)
- Central nervous system vascular disorders (SMQ)
- Infections and infestations (SOC)
- Quality of life decreased (PT)

4.7 Interim Analyses and Data Monitoring

4.7.1 Interim Analysis

No formal interim analysis for the primary endpoint is planned. An interim analysis for secondary endpoint OS will be conducted at the time of primary completion analysis.

4.7.2 Independent Data Monitoring Committee (DMC)

A DMC will be instituted to ensure ongoing safety of study participants with respect to a risk/benefit assessment during periodic data review meetings. The DMC will operate independently of the Sponsor and Investigators.

4.8 Changes to Protocol-planned Analyses

Section #	Description of Change	Brief Rationale
4.3.6	Used an increase of 2 or more points in the WPS score from nadir for the definition of pain progression. Added initiation of short- or long-acting opioid use for malignant disease for ≥7 consecutive days to the definition of pain progression. Used WPS ≥5 in the definition of pain progression.	Change from baseline to Nadir in the definition of pain progression: based on FDA feedback on ARASENS study. Based on FDA feedback to include opioid use for malignant disease for ≥7 consecutive days during the treatment in the definition of time to pain progression. Change of WPS ≥ 5 : based on FDA feedback on ARASENS study, and the publication (Atkinson et al. (2010))

5. Sample Size Determination

Assuming a one-sided alpha of 0.025 for rPFS, a hazard ratio of 0.625 and a randomization ratio of 2:1 between the experimental and control arms, 214 events are required to achieve a power of 90% for a statistically positive outcome.

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

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

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

6. Supporting Documentation

6.1 Participant Disposition

The number of participants enrolled and included in each population will be tabulated by country/region, and center. The number of participants starting, completing, and discontinuing together with the primary reason for discontinuing of the Screening, Treatment, Active follow-up, and Long-term follow-up periods will be presented overall and by treatment arm, except for the Screening period. Number of participants currently on treatment at the primary analysis cut-off will also be summarized by treatment arm. Disposition of screening will be summarized for all enrolled participants, and disposition of other periods will be summarized for the FAS.

In addition, the number of participants with important protocol deviations will be presented by deviation coded term, treatment arm and overall. Number of participants affected by COVID-19 pandemic related study disruption will be provided.

6.2 Demography and Other Baseline Characteristics

Descriptive summaries of demographics and baseline characteristics are presented by treatment arm and overall for the FAS population. Comparability of the treatment arms with respect to demographics and baseline characteristics is assessed using descriptive summaries.

For these tables, the summaries refer to the randomization baseline by default, i.e., the last non-missing value on or before the date of randomization.

The following demographic data will be summarized:

- Age at screening (years)
- Age category (<65, 65–74, 75–84, ≥85 years)
- Geographical region (Asia (China, India, Taiwan), Latin America (Brazil, Chile, Peru), Europe and Rest of the world (Australia, Canada, Spain, Lithuania, Latvia, New Zealand, Russia, Ukraine, and South Africa))
- Race (White, Asian, Black or African American, Other)
- Ethnicity
- Weight at baseline (kg)
- Body Mass Index (BMI) (kg/m^2) (<20, 20 to <25, 25 to <30, ≥30)
- Hepatic function at baseline
    - Normal: Total bilirubin and AST ≤ upper limit of normal (ULN)
    - Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (total bilirubin ≤ ULN and AST > ULN)
    - Moderate impairment: Total bilirubin > 1.5 to 3 x ULN, any AST
    - Severe impairment: Total bilirubin > 3 x ULN, any AST

- Renal function – eGFR at baseline (normal, mild impairment, moderate impairment, severe impairment)

The following baseline characteristics will be summarized:

- Histology
- Grading (AJCC) at initial diagnosis
- Visceral metastases assessed by central review (present or absent) and prior local therapy (Yes or No) from both IWRS.
- Time from initial diagnosis of metastases to the date of the first actual dose of darolutamide or placebo (months)
- Time from initial diagnosis of prostate cancer to the date of the first actual dose of darolutamide or placebo (months)
- Stage of prostate cancer (TNM Classification) at initial diagnosis
- Gleason score prostate cancer (<8, ≥8) at initial diagnosis of prostate cancer
- Status of primary tumor at study entry
- Stage of prostate cancer (TNM Classification) at study entry
- Extent of metastatic disease at study entry (Non-regional lymph nodes metastases only, Bone metastases with or without lymph node metastases, Visceral metastases with or without lymph node metastases or with or without bone metastases), from eCRF
- Prior local radiotherapy and/or prostatectomy (yes, no)
- PSA (ug/L) at baseline (<median of overall population, ≥median of overall population) - central laboratory
- Testosterone (ng/mL) at baseline - central laboratory
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) at baseline
- Disease volume at baseline (high, low)

  Participant will be considered to have a high disease volume at baseline if one of the 3 following criteria per central imaging data from at least one of the reviewers are met at baseline:

  1. presence of visceral metastases
  2. ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis
  3. Presence of Superscan

Participant with no above criteria will be considered to have a low disease volume at baseline.

- ALP (U/L) at baseline

6.3 Medical History

For data coding, Medical Dictionary for Regulatory Activities (MedDRA v. 25.1 or later) will be used for medical history. Medical history findings (i.e., previous diagnoses, diseases or surgeries) not pertaining to the study indication, start before signing of the ICF and considered relevant to the study will be presented for each MedDRA Primary System Organ Class (SOC) and Preferred Term (PT) by treatment arm and overall for the FAS.

6.4 Prior and Concomitant Medication and Procedures

Prior therapy is defined as all medications taken before the start of darolutamide or placebo treatment. Concomitant therapy is defined as all medications taken between the start of darolutamide or placebo treatment and the last dose date of darolutamide or placebo. Follow up therapy is defined as all medications started after the last dose date of darolutamide or placebo.

Prior, concomitant and post-treatment medications will be coded by the World Health Organization Drug Dictionary (WHO-DD). Prior and concomitant medication will be summarized based on Anatomical-Therapeutic-Chemical (ATC) Class (level 1, which is the first character from the WHO-DD code) and ATC Sub-class (level 2, which is the first 3 characters from the WHO-DD code). Note that the same medication can appear more than once in the table as it can have several ATC codes.

All participants must receive an ADT of the Investigator's choice (LHRH agonist/antagonists or orchiectomy) as standard therapy started ≤12 weeks before randomization, on a continuous basis. The duration of ADT received within 12 weeks from randomization by geographical region will be provided.

The following frequency tables will be provided by treatment arm and overall for the FAS:

- Concomitant medications excluding ADT: frequency of participants for each drug category
- Prior, and concurrent opioid treatment for malignant disease: frequency of participants
- Prior ADT started ≤12 weeks before randomization: summary of duration
- Prior and subsequent systemic anti-cancer therapy: frequency of participants for each drug category
- Prior local treatment for prostate cancer at study entry (by prostatectomy, surgery, TURP, other, radiation, no surgical treatment and no radiation)
- Prior, concomitant and follow up radiotherapy: frequency of participants
- Concomitant prostate cancer related-invasive procedures (defined in Appendix 8.9): frequency of participants by grouped term and procedure.

7. References

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2. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016;34(12):1402-18.
3. Robins JM, Tsiatis AA Correcting For Non-Compliance in Randomized Trials Using Rank Preserving Structural Failure Time Models. Commun. Statist.-Theory Meth. 1991; 20(8):2609-2631.
4. Branson M, Whitehead J: Estimating a Treatment Effect in Survival Studies in Which Patients Switch Treatment. Statistics in Medicine 2002, 21:2449-2463.

8. Appendix

8.1 RECIST 1.1 Criteria

This study will use RECIST 1.1 criteria for assessment of extra-skeletal malignant lesions. Metastatic bone lesions will be assessed in accord with PCWG3 criteria ; see Appendix Section 8.2).
RECIST 1.1 criteria:

Definition of Measurable disease:

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

Non-measurable disease

All other lesions are considered non-measurable. This includes small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) and also truly non-measurable lesions, such as: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung.
Bone lesions, cystic lesions and lesions previously treated with local therapy require particular comment:
Bone lesions: (Note: not assessed by RECIST 1.1 in the current study)

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

Cystic lesions:

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

Lesions with prior local treatment:

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

Target lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where participants have only 1 or 2 organ sites involved a maximum of 2 and 4 lesions respectively will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible

measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the **baseline sum diameters**. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective change in the measurable dimension of the disease. Optimally, lesions selected as target (measurable) lesions should not be biopsied. Additional guidance will be provided to the site on decisions about performing biopsies on potential target lesions when only one potential target lesion exists at baseline.

Non-target lesions

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

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

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

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

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

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

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

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

To achieve unequivocal progression in participants with measurable disease on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target

disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal.
In the absence of measurable disease, the same general concepts apply here as noted above.
The above text descriptions of the visit/time point response are logically equivalent to Table 8–1 below.

Table 8–1 RECIST 1.1 - Time Point Response for participants with target and non-target lesions

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

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

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

Response duration

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

Stable disease duration

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

8.2 Prostate Cancer Working Group 3 Criteria for Bone Metastases

In this study, the PCWG3 criteria will be used for bone metastases only. All extra-skeletal metastatic disease will be assessed by RECIST 1.1 (Appendix 8.1).

Details of the Prostate Cancer Working Group 3 Criteria may be found:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4872347/pdf/JCO642702.pdf
^{99m}Tc-phophonate whole body planar bone scans are to be used for assessment of bone disease.

Bone lesion response types per PCWG3:

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

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

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

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

8.3 Systemic Anticancer Therapy

Systemic anticancer therapy treatment was selected from “Systemic Anti-Cancer Therapy during Follow-Up” eCRF pages or “Prior and Concomitant Medication” eCRF pages or Prior and Concomitant Androgen Deprivation Therapy eCRF pages below in CM dataset.

- ATC code class L (antineoplastic and immunomodulating agents): L01 Antineoplastic agents, L02 endocrine therapy, L03 immunostimulants and L04 immunosuppressants.
- ATC code class V10 (radiopharmaceuticals).
- ATC code class G (genito urinary system and sex hormones): G03CA, G03CB,
- ATC code class V (various): V03AX, V98.
- If the WHO-DD drug record number is 062951(ABIRATERONE), 900315 (ANTINEOPLASTIC AGENTS), 012711 (BICALUTAMIDE), 082361 (RADIUM RA 223 DICHLORIDE).
- If ATC code or code class is same as any above, but the WHO-DD drug record number is 093203 (MARSDENIA TENACISSIMA STEM), 000826 (MEGESTROL ACETATE), 007269 (LEUPRORELIN ACETATE), 007321 (GOSERELIN ACETATE), 009759 (TRIPTORELIN EMBONATE), 017648 (DEGARELIX ACETATE), 010277 (UBENIMEX), 017660 (THYMALFASIN), 901166 (OTHER THERAPEUTIC PRODUCTS), 007716 (buserelin), 000454 (ESTRADIOL), 132744 (ETHINYLESTRADIOL; NORELGESTROMIN) then do not consider as anticancer therapy.

The sponsor’s assessment of anticancer therapy based on the ATC codes is presented in a supplementary document and used in the analyses.

Subsequent systemic anticancer therapy is defined as the systemic anticancer therapy starting on or after first study treatment.

8.4 BPI-SF

1903

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

Subject's Initials : _____

Study Subject #: ☐☐☐☐

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

Pt: _____

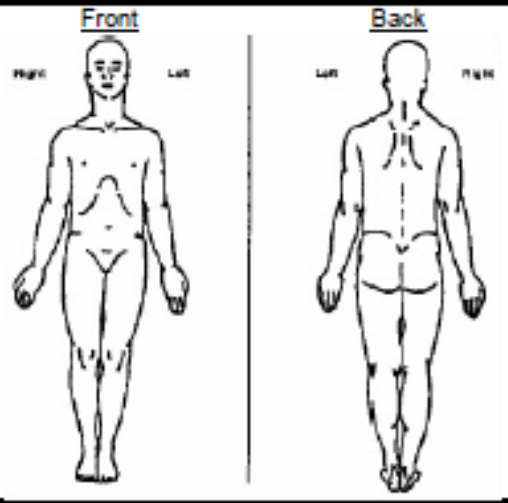
Revision: 07/01/05

Brief Pain Inventory (Short Form)

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

☐ Yes ☐ No

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



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

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
No Pain — Pain As Bad As You Can Imagine

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

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
No Pain — Pain As Bad As You Can Imagine

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

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
No Pain — Pain As Bad As You Can Imagine

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

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
No Pain — Pain As Bad As You Can Imagine

Page 1 of 2

1903

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

Subject's Initials: _____

Study Subject #:

Study Name: _____

Protocol #: _____

Pt: _____

Revision: 07/01/05

PLEASE USE BLACK INK PEN

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

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

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

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

A. General Activity

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

B. Mood

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

C. Walking ability

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

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

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

E. Relations with other people

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

F. Sleep

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

G. Enjoyment of life

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

8.5 FACT-P (Version 4)

FACT-P (Version 4)

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

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

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

FACT-P (Version 4)

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

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

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

FACT-P (Version 4)

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

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
M2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
M3	I am able to have and maintain an erection	0	1	2	3	4

FACT-P Scoring Guidelines (Version 4)

Instructions:
1. Record answers in "item response" column. If missing, mark with an X

2. Perform reversals as indicated, and sum individual items to obtain a score.

3. Multiply the sum of the item scores by the number of items in the subscale, and then divide by the number of items answered. This produces the subscale score.

4. Add subscale scores to derive total scores (TOI, FACT-G & FACT-P).

5. The higher the score, the better the QOL.

Subscale	Item Code	Reverse item?		Item response	Item Score
PHYSICAL	GP1	4	-	_____	=_____
WELL-BEING	GP2	4	-	_____	=_____
(PWB)	GP3	4		_____	=_____
	GP4	4	-	_____	=_____
Score range: 0-28	GP5	4	-	_____	=_____
	GP6	4	-	_____	=_____
	GP7	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____= **PWB subscale score**

SOCIAL/FAMILY	GS1	0	+	_____	=_____
WELL-BEING	GS2	0	+	_____	=_____
(SWB)	GS3	0	+	_____	=_____
	GS4	0	+	_____	=_____
Score range: 0-28	GS5	0	+	_____	=_____
	GS6	0	+	_____	=_____
	GS7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____= **SWB subscale score**

EMOTIONAL	GE1	4	-	_____	=_____
WELL-BEING	GE2	0	+	_____	=_____
(EWB)	GE3	4	-	_____	=_____
Score range: 0-24	GE4	4	-	_____	=_____
	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 6: _____
Divide by number of items answered: _____= **EWB subscale score**

FUNCTIONAL	GF1	0	+	_____	=_____
WELL-BEING	GF2	0	+	_____	=_____
(FWB)	GF3	0	+	_____	=_____
Score range: 0-28	GF4	0	+	_____	=_____
	GF5	0	+	_____	=_____
	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____= **FWB subscale score**

FACT-P Scoring Guidelines (Version 4) – Page 2

Subscale	Item Code	Reverse item?		Item responds	Item Score
PROSTATE	C2	4	-	_____	=_____
CANCER	C6	0	+	_____	=_____
SUBSCALE	P1	4	-	_____	=_____
(PCS)	P2	4	-	_____	=_____
	P3	4	-	_____	=_____
Score range: 0-48	P4	0	+	_____	=_____
	P5	0	+	_____	=_____
	P6	4	-	_____	=_____
	P7	4	-	_____	=_____
	BL2	4	-	_____	=_____
	P8	4	-	_____	=_____
	BL5	0	+	_____	=_____

Sum individual item scores: _____

Multiply by 12: _____

Divide by number of items answered: _____=**PC Subscale score**

To derive a FACT-P Trial Outcome Index (TOI):
Score range: 0-104
_____ + _____ + _____ =_____=**FACT-P TOI**
(**PWB** score) (**FWB** score) (**PCS** score)

To Derive a FACT-G total score:
Score range: 0-108
_____ + _____ + _____ + _____=_____=**FACT-G Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score)

To Derive a FACT-P total score:
Score range: 0-156

_____ + _____ + _____ + _____ + _____ =_____=**FACT-P Total score**

(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score) (**PCS** score)

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.

8.6 Special topic AE definitions

Table 8–2 Special topic AE definitions

Grouped term	MedDRA search criteria for special topics
Bone fractures excluding pathological fractures	HLT: Fractures and dislocations NEC (without PTs: Joint dislocation, Joint dislocation pathological) HLT: Limb fractures and dislocations (without PT: Radial head dislocation) HLT: Pelvic fractures and dislocations HLT: Skull fractures, facial bone fractures and dislocations HLT: Spinal fractures and dislocations (without PT: Dislocation of vertebra) HLT: Thoracic cage fractures and dislocations (without PT: Dislocation of sternum) Exclude PT pathological fractures
Diabetes mellitus and hyperglycemia	MLG: Hyperglycemia PTs: Diabetes mellitus; Diabetes mellitus inadequate control; Diabetic metabolic decompensation; Type 2 diabetes mellitus; Diabetic ketoacidosis
Fall*	PTs Fall; Accident
Fatigue/ asthenic conditions	MLG: Decreased general strength and energy PTs: Lethargy; Chronic fatigue syndrome; Malaise
Weight decreased	MLG: Weight decreased
Rash	MLG: Rash MLG: Skin erythema PT: Dermatitis
Seizure	MLG: Seizures
Hypertension	MLG: Hypertension, PTs Hypertensive crisis, Hypertensive emergency
Vasodilatation and flushing	MLG: Vasodilatation and flushing
Mental impairment disorders	HLGT: Mental impairment disorders
Depressed mood disorders	HLGT: Depressed mood disorders and disturbance
Breast disorders/gynecomastia	HLGT: Breast disorders
Cardiac disorders	HLGT: Cardiac arrhythmias HLGT: Coronary artery disorders HLGT: Heart failures
Cerebral ischaemia	MLG: Cerebral infarction and stroke not specified as hemorrhagic or ischemic MLG: Cerebral ischemic infarction and stroke PT: Cerebral ischaemia, Transient ischaemic attack
Cerebral and intracranial hemorrhage	MLG: Cerebral and intracranial hemorrhage
Interstitial lung disease	SMQ: Interstitial lung disease (narrow search)

MLG: MedDRA Labeling Grouping; PT: Preferred Term; HLT: High Level Term; HLGT: High Level Group Term; SMQ: Standardized MedDRA Query

*Based on review of verbatims the search criteria for “Fall” was extended by the PT “Accident”.

8.7 Bone health agent (BHA)

Bone health agent were selected in CM dataset, using ATC codes:

M05BA
M05BC (bone morphogenic protein)
M05BB: Bisphosphonates
M05BX: Denosumab

8.8 Imputation rule for partial missing Adverse Event/ Concomitant medication dates

Table 8–3 Imputation rule for partial missing dates

Partial Dates Imputation Rule	Impute partial AE/CM Start Date	Impute partial AE/CM Stop Date
The day missing only	IF AESTDT year and months is same as TRTSDT year and months, then impute AESTDT= TRTSDT	IF AEENDT year and months is same as last known alive date (LKAD) year and months, then impute AEENDT= LKAD
	ELSE IF AESTDT year and month is before TRTSDT year and months, then AESTDT= last date of the months	ELSE impute AEENDT= last date of the months
	ELSE IF AESTDT year and month is after TRTSDT year and months, then AESTDT= first date of the months	
Both day and months missing	IF AESTDT year is same as TRTSDT year, then impute AESTDT=TRTSDT	IF AEENDT year is same as last known alive date (LKAD) year, then impute AEENDT= LKAD
	ELSE IF AESTDT year is before TRTSDT year, then impute AESTDT=31DECYYYY	ELSE impute AEENDT=31DECYYYY
	ELSE IF AESTDT year is after TRTSDT year , then impute AESTDT=01JANYYYY	
Completely missing	No need to impute, try to query the sites by DM	No need to impute, try to query the sites by DM
Additional criteria to meet	1. AE/CM start date <= AE/CM stop date 2. The imputed dates <= last known alive date (LKAD) 3. If TRTSDT is missing, use RANDDT as reference date	

8.9 Prostate cancer-related invasive procedure

Prostate cancer-related invasive procedure is defined as any procedure needed for alleviation of symptoms, signs or findings caused by progression of prostate cancer (e.g., catheterization of the bladder, percutaneous drainage of hydronephrosis, palliative electro resection of the prostate, etc.).

The sponsor's assessment of prostate cancer-related invasive procedure is presented in a supplementary document and used in the analysis.

8.10 Prior local radiotherapy and/or prostatectomy

Prior local radiotherapy and/or prostatectomy is defined as any prior local radiotherapy for prostate, prostatectomy and TURP.

The sponsor's assessment of prior local radiotherapy and/or prostatectomy/TURP is presented in a supplementary document and used in the analysis.