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Title Page

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Protocol Number: 21516

Compound Number: BAY 1841788 / darolutamide / ODM–201

Short Title: Open-label external control arm study of darolutamide plus ADT in men with mHSPC

Acronym: ARASEC

Sponsor Name: Bayer HealthCare Pharmaceuticals Inc.

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

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This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.
The approval of the Statistical Analysis Plan is documented in a separate signature document.

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Version History

This Statistical Analysis Plan (SAP) for study protocol 21516 is based on the protocol Version 2.0 dated 15 JUN 2021.

SAP Version	Date	Change	Rationale
1.0	05 AUG 2022	Not Applicable	Original version
2.0	12 JUL 2023	• 5.3.2: Removed 'treatment group' from listings except for the primary efficacy listing and added in age and race. This is because only one cohort is presented and the treatment group will be the same for all patients. • 5.6.2: clarified that TEAEs leading to discontinuation of treatment will be provided. • 5.6.3: correction that summaries of worst CTCAE will be provided by event category and NCI CTCAE term instead of by parameter. • 5.7.2, 6.1: standardized wording to ECOG performance status instead of score. • 6.3: Changed PD listing to present important PDs only, per sponsor standards. • Minor typographical corrections and clarifications. • IPTW analysis added.	Minor corrections and clarifications following TLF shell development
3.0	19 JUL 2023	• 4: ME-FAS for CHAARTED participants modified to include participants with missing covariates. Participants with missing covariate data will be excluded from the matching, but not the ME-FAS. • 5.3.3: Details of sensitivity analysis for primary endpoint with propensity scores calculated treating missing Gleason score as a category instead of exclusions added	Addition of sensitivity analyses for primary and secondary endpoints, addition of safety analyses. Update to definition of ME-FAS for CHAARTED participants.

		• 5.4.1.3: Details of sensitivity analysis for secondary endpoints with propensity scores calculated treating missing Gleason score as a category instead of exclusions added • 5.6.2: the following tables of adverse events by SOC and PT added: - TEAE's by age groups - Most common TEAEs (≥5% of participants) - TEAEs related to study drug by age groups - Most common study drug related TEAEs (≥5% of participants) - Treatment emergent SAEs by age groups - Most common treatment emergent SAEs (≥5% of participants). • 5.6.2: table of TEAEs related to study drug by SOC, PT and maximum CTCAE grade added. • 5.6.2: Added sentence 'Analysis of Special Topics, as defined for the mHSPC darolutamide ARANOTE study, will be provided for TEAEs, SAEs and Drug related TEAEs.' • 5.6.2: table of TEAEs related to study drug by SOC, PT and worst outcome added. • 5.6.2: table of TEAEs related to study drug per 100 person-years added. • 5.6.3: bilirubin and glucose added to chemistry tests. • 6.4: CHAARTED ITT analysis set removed from descriptive summary and medical history tables.	

1. Introduction

Analyses to evaluate the efficacy and safety of darolutamide in combination with Androgen Deprivation Therapy (ADT) versus ADT alone as treatment for men diagnosed with Metastatic Hormone-sensitive Prostate Cancer (mHSPC) are described. The study will use a matched control arm from the ADT alone arm from the CHAARTED trial. The matching will be conducted by analysts who are blinded to the post-baseline efficacy outcome data and the actual use or dosing of the ARASEC study

This SAP describes the analysis of the study at two data-cuts expected after about 12 months for the Progression Free Survival (PFS) primary endpoint, Prostate Specific Antigen (PSA) related endpoints and safety, and 24 months after the end of enrollment for the remaining endpoints. Two matching exercises will be conducted, one after about half the participants are enrolled and a final matching after the end of enrollment. Table, figure and listing specifications are contained in a separate document. No group sequential statistical interim analysis will be performed. Any changes to the protocol-planned analyses will be documented in Section 6.14. This statistical analysis plan will be finalized prior to the unblinding of the sponsor to the eligible participants in the Matched Population (as detailed in Section 4).

1.1 Objectives and Endpoints

The purpose of this study is to evaluate the efficacy and safety of darolutamide in combination with ADT versus ADT alone, using a matched control arm from the CHAARTED trial as treatment for men diagnosed with Metastatic Hormone-sensitive Prostate Cancer (mHSPC). The primary hypothesis of this study is that darolutamide in combination with ADT is superior to ADT alone in terms of progression-free survival (PFS).

Objectives	Endpoints
Primary	
• To assess if the addition of darolutamide to ADT compared with ADT alone would result in superior clinical efficacy in participants with mHSPC by superior PFS	• PFS (PFS is defined as the time interval from enrollment to PSA progression, clinical progression or death, whichever occurs first. Clinical progression is defined as increasing symptomatic bone metastases, radiographic progression per Response Evaluation Criteria In Solid Tumors (RECIST) criteria (v. 1.1) for soft tissue metastases and Prostate Cancer Clinical Trials Working Group (PCWG3) criteria for bone metastases, or clinical deterioration due to cancer per investigator's opinion)
Secondary	
• To assess if the addition of darolutamide to ADT compared to	• Overall survival (OS) (defined as the time from the date of enrollment

ADT alone can prolong overall survival	until death resulting from any cause or the date last known alive)
• To assess radiographic progression-free survival in participants who received darolutamide plus ADT	• Radiographic Progression-free survival (rPFS) (defined as the time from enrollment to investigator-assessed radiographic progression RECIST criteria (v. 1.1) for soft tissue metastases and PCWG3 criteria for bone metastases or death, whichever occurs first)
• To assess if the addition of darolutamide to ADT compared to ADT alone can increase the time to castration-resistant prostate cancer (CRPC)	• Time to CRPC (Defined as the time from enrollment until documented clinical or PSA progression with a testosterone level of less than 50 ng per deciliter or documented medical castration or surgical castration])
• To assess the complete PSA response rate at 6 months in the ADT + darolutamide arm vs ADT alone	• Complete PSA response rate at 6 months from enrollment date (Defined as a PSA level of less than 0.2 ng per milliliter on two consecutive measurements at least 4 weeks apart)
• To assess the frequency of adverse events (AEs) and the safety of darolutamide combined with ADT versus ADT alone	• Adverse Events will be assessed by National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) (v. 5.0)

Abbreviations: ADT = androgen deprivation therapy; PFS = progression-free survival; mHSPC = metastatic hormone-sensitive prostate cancer; RECIST = Response Evaluation Criteria In Solid Tumors (v. 1.1); CRPC = castration-resistant prostate cancer; PSA = prostate specific antigen; OS = overall survival; NCI = National Cancer Institute; CTCAE = Common Terminology Criteria for Adverse Events

a Enrollment for the active arm of this study is defined as the date investigator confirms the participant meets all inclusion and exclusion criteria. This date may be used for matching with the control arm and is considered equivalent to randomization date from the CHAARTED study, thus, enrollment for the control arm is defined as the date of randomization of participants in the CHAARTED study.

b PSA progression is defined as when the PSA demonstrates an increase that is more than 50% of nadir, taking as reference the lowest recorded PSA level since starting ADT. Two consecutive increases must be documented with each measurement obtained at least two weeks apart. On occasions, there may be an intermediate fluctuant value. This will **not** restart the evaluation period so long as the intermediate value was not below the previous nadir.

The date of first recorded increase (not defeated by a subsequent drop in PSA level to create a new nadir) will be deemed the date of progression.

If a participant achieves a PSA that is less than 4 ng/mL, the confirming increase must reach a value that is more than 4.0 ng/mL (the unconfirmed and additional intermediate increases may be a value that is less than 4.0 ng/mL, but greater than 50% of nadir since starting ADT).

If a participant's nadir is less than 2 ng/mL, the first time the PSA reaches a value greater than 50% of nadir since starting ADT **and** is at least 2 ng/mL will be the date of first progression. However, this progression must be confirmed by a PSA value that is more than 4.0 ng/mL with no intervening declines below 2 ng/mL.

Progression will be declared if participant has documented to have a testosterone less than 50 ng/dL. In cases where a testosterone level has not been obtained and participant has not had an orchiectomy (as detailed in the study calendar), PSA progression will be deemed if participant had a documented rise in PSA on LHRH analogue therapy.

1.2 Study Design

This is a phase 2 open label single arm study using an external control arm, to assess if the addition of darolutamide to ADT provides superior efficacy in terms of progression-free survival (PFS), as compared to ADT alone for men diagnosed with mHSPC. This study is not blinded and participants are not randomized.

The primary endpoint is PFS. Approximately 200 mHSPC participants will receive darolutamide plus ADT in the ARASEC active treatment arm. The control arm for the study will be derived from the participants treated with ADT alone in the CHAARTED trial using a matching approach.

All participants will receive darolutamide 600 mg bid plus ADT. The study duration will be from the first participant's, first visit until study completion. The study completion is defined as when either the primary endpoint has been met or all participants have been followed (including survival follow-up) for at least 2 years after enrollment, whichever occurs later, unless the participant withdrew, died or was lost to follow-up. Dose modifications, interruptions and reductions are handled per section 6.6 of the protocol.

The study will comprise the following consecutive periods: Screening, Treatment period, Active Follow–up period and Survival Follow–up period.

Screening period:

After the participant has signed the informed consent, the screening period will begin from the date of signed informed consent. Participant screening must occur within 28 days prior to enrollment, during which all study-related procedures and evaluations will be performed in order to establish participant eligibility. Enrollment will take place in the IWRS, where the participant will receive a unique participant ID.

Enrolled participants will start darolutamide administration twice daily in addition to ADT within 3 days since enrollment.

Treatment period:

Participants will receive darolutamide in addition to ADT. The treatment period is defined as the time from the administration of first dose of darolutamide until clinical progression, unacceptable toxicity, withdrawal of consent, investigator's decision to stop therapy for the participant, participant decision to stop therapy, sponsor's decision to terminate the study, or death. All participants will receive and remain on a stable regimen of ADT (Luteinizing hormone releasing hormone agonist /antagonists or surgical castration) at the discretion of the investigator.

End of Treatment Visit:

End of Treatment (EOT) visit will be conducted 30 days (+ 7 days) after the last treatment of darolutamide. During the EOT visit, procedures to monitor participant's health, to identify potential toxicities, to assess efficacy should be performed (protocol section 1.3).

If a participant had PSA and/or clinical progression, these participants will be followed up in the survival follow-up period. Participants without progression will be followed up in the active follow-up period.

Active Follow–up period:

After EOT, the participants who discontinued darolutamide treatment for reasons other than PSA progression or clinical progression (including radiographic progression or symptomatic progression) will be followed during the active follow-up period until PSA progression or clinical progression. During the active follow–up period, the following assessments will be performed as defined in protocol section 1.3:

- Assessment of progression:
  - Serum PSA
  - Testosterone
  - Clinical progression assessments
  - Radiographic progression
- AEs/serious AEs (SAEs) (up to 30 days after end of treatment visit)
- Subsequent antineoplastic therapy.

Survival Follow-up period:

Participants who had PSA progression or clinical progression will enter survival follow-up period. Participants who are on darolutamide treatment or are in the Active Follow-up at the time of primary endpoint data cutoff will enter Survival Follow-up period until End of Study.

During the survival follow–up period, the following assessments will be performed as defined in protocol section 1.3:

Related SAEs with concomitant medications received

- Subsequent antineoplastic therapy
- Survival status
- In case that a participant did not experience radiographic progression and did not start new antineoplastic treatment, tumor imaging assessment for radiographic progression should continue in the survival follow-up.

Section 6.6 of the study protocol contains rules/procedures for dose modifications and dose interruptions. The primary analysis will be conducted after 161 PFS events are tallied across the ARASEC cohort and the matched controls at a similar follow-up duration as described in Section 5 of this SAP.

2. Statistical Hypotheses

The primary hypothesis of this study is that darolutamide in combination with ADT is superior to ADT alone in terms of progression-free survival (PFS) by testing the following null hypothesis under the proportional hazards model against an alternate of a hazard ratio less than 1 using a one-sided alpha level of 0.025.

$$H0: h_A(t)/h_C(t) = 1 \text{ vs } H1: h_A(t)/h_C(t) < 1,$$

where $h_A(t)$ and $h_C(t)$ are the hazards over time t in the matched ARASEC and CHAARTED control arms, respectively.

3. Sample Size Determination

Assuming a one-sided alpha of 0.025, power of 90%, and a hypothetical enrollment ratio of 1:1 between the experimental and external control arms, approximately 161 PFS events across the two arms are required to detect an increase in median PFS relative to the matched control, if the HR is 0.60. With exponential distribution, this HR translates into a 66% increase in PFS (from 11.6 months to 19.3 months).

A total of 200 participants will be enrolled to receive darolutamide plus ADT to account for dropouts and mismatches and matched with 394 external control arm participants with a 1:1 ratio. This matching will be conducted by analysts using baseline data who are agnostic to ARASEC outcomes. Assuming a final match rate of ~80%, approximately 160 participants per arm (a total of 320 participants) will be available in the matched population for the endpoint comparisons. Additional patients may be enrolled in the event of a lower matching rate.

The sample size calculations provided here are based on the above-mentioned expectations. The actual sample size and matching ratio may differ if a larger number of participants have baseline profiles different from those available in CHAARTED. Any such changes will be made before the unblinding of the ARASEC outcome data to analysts and will retain the specified one-sided 0.025 level false positive rate.

4. Analysis Sets

The populations for analyses will be the Match Eligible Full Analysis Set (ME-FAS) and the Matched Full Analysis Set (M-FAS) as Tabled below. Matching is further defined in Appendix 1 and will use baseline factors listed in the appendix which are likely to affect the outcome and are available in the Datasphere for the CHAARTED study.

Population	Description
Match Eligible Full Analysis Set (ME- FAS)	Participants who sign Informed Consent and take at least one dose of darolutamide in the ARASEC cohort will be considered eligible for matching. For CHAARTED the eligible patients will be the control participants in the intention-to-treat (ITT) population. In ARASEC approximately 200 participants are expected to be eligible.
Matched Full Analysis Set (M-FAS)	The M-FAS will include all participants from the ME-FAS who are matched 1:1. Participants without a match will be removed. Analysts will be agnostic to post baseline efficacy data when conducting the match.

Date of enrollment for the active arm of this study is defined as the date investigator confirms the participant meets all inclusion and exclusion criteria. This date may be used for matching with the control arm and is considered equivalent to randomization date from the CHAARTED study, thus, date of enrollment for the control arm is defined as the date of randomization of participants in the CHAARTED study. All control participants in the CHAARTED ITT population will be considered 'enrolled' for this study.

A number of participants have missing covariate assessments in both cohorts and the ME-FAS will be obtained as indicated in the table above without these participants excluded, but with these exceptions removed from analysis in the participant matching descriptive table, the histogram, and the inverse probability of treatment weighting (IPTW) sensitivity analyses to allow for the computation of the propensity score. For all other tabled information the ME-FAS will use all participants. The M-FAS population will be the primary population for baseline summaries and for all efficacy analyses described and will be presented together for the data items of interest shared across the two cohorts. Additional sensitivity analyses treating missing Gleason score as a category instead of exclusions are described in Sections 5.3.3 and 5.4.1.3. Safety analyses for darolutamide participants in ARASEC M-FAS will be presented next to those for the ARASEC ME-FAS.

Baseline data relating to the variables used for matching, and primary and secondary efficacy endpoint data will be available from the CHAARTED study, and the primary and secondary efficacy analyses will be performed on the M-FAS. All other analyses, including listings from the ARASEC eCRF data, will be performed on ARASEC ME-FAS, as only data from the ARASEC cohort will be available for the other analyses.

Final decisions regarding the assignment of participants to analysis sets will be made during the review of study data and documented in the final list of important deviations, validity findings and assignment to analysis set(s). Important deviations may lead to the exclusion from analysis sets as per the protocol deviation analysis plan.

A summary of the number and percentage of participants in each analysis population will be presented for all enrolled participants from both the ARASEC and CHAARTED cohorts and in total, with denominators based on the number of enrolled participants in each cohort.

A by-participant listing of analysis population details will be presented for all enrolled participants from both the CHAARTED and ARASEC cohorts, including the participant identifier, age, race, cohort (ARASEC/CHAARTED), an indication of inclusion/exclusion from each analysis set and the reason for exclusion. If participant data was partially excluded from an analysis set, details of the data and visit that has been excluded will appear on this listing.

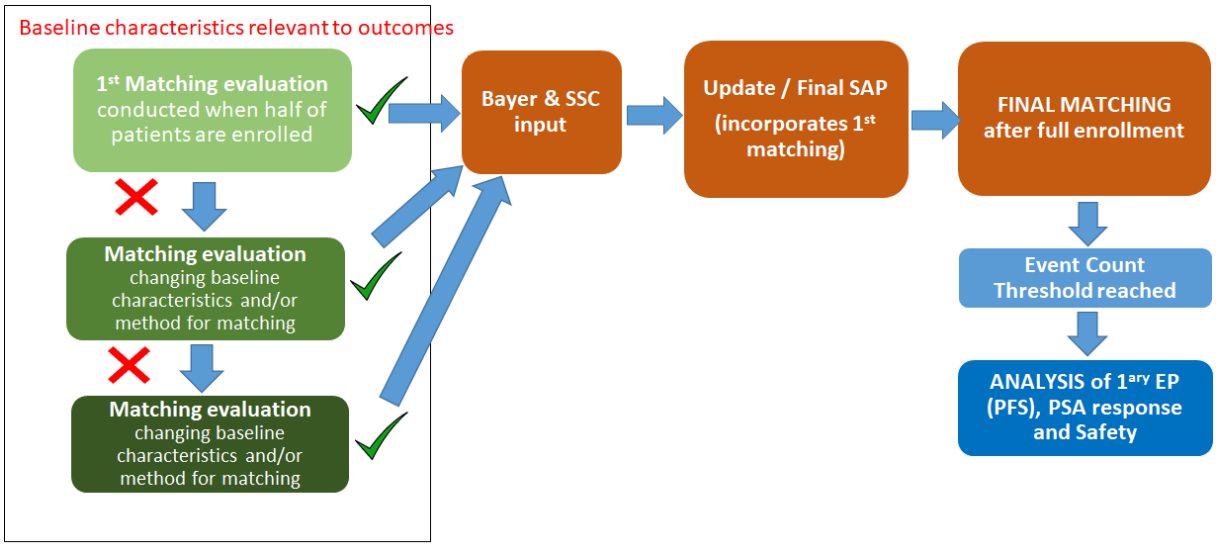
5. Statistical Analyses

5.1 General Considerations

The matching to determine the Matched Full Analysis Set (M-FAS) will be conducted independently by an external vendor using baseline data across the two cohorts of eligible participants. The separation of the matching analysis from the outcome analyses will be achieved though the following procedure:

- Complete baseline data will be provided to the Matching analysts from the CHAARTED and the ARASEC study shortly after the last ARASEC participants is enrolled after all available baseline data for enrollees has been entered and all data queries for this data has been resolved. A matching exercise will also be conducted part-way through enrollment to gauge actual matching rates in order to consider increases in enrollment in the event of a projected short-fall. No post-baseline outcome or dosing data will be shared with the Matching analysts at this time.
- The matching analysts conducts a preliminary matching based on baseline factors likely to affect outcome and provides the sponsor with key aggregate baseline tables by the preliminary matched cohorts, as well as aggregate statistics on matching diagnostics, without providing any participant level information on matching.
- The sponsor team in collaboration with the Steering Committee (SC) evaluates aggregate participant data and diagnostics and provide the analysts feedback on the adequacy of the matching and the model.

The analysts make any changes needed and forward the final key baseline summaries and matching diagnostics and freeze the participant level analysis data sets flagging participants in the Matched Population. The schema for the matching is depicted below.



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

'Baseline' is defined as the last measurement prior to treatment start. 'End of Treatment' is defined as the visit 30 days (+7 days) after the last dose of darolutamide. 'Study Day' will be calculated relative to the date of baseline such that Study Day = Assessment Date – Date of Baseline +1. For analyses of change from baseline, subjects with missing baseline values will be excluded.

All visit-based summaries using data recorded on the eCRF will use analysis visits. All post enrollment scheduled and unscheduled visits (excluding premature discontinuation visit), will be mapped to an appropriate analysis visit per the table below.

eCRF visit	Target day	Actual assessment day
Week 1 Day 1 (Baseline)	D1	D1
Post-Baseline Visits (every 12 weeks)	Every 12 weeks (84 days) after the previous visit	Every 12 weeks (84 days), ± 7 days after the previous visit
EOT Visit	30 days after last dose of darolutamide	30 days (+7 days) after last dose of darolutamide
Active Follow–up Visits	Every 12 weeks after EOT visit until PSA or clinical progression	Every 12 weeks after EOT visit until PSA or clinical progression
Survival Follow-up Visits	Every 12 weeks until end of study	Every 12 weeks until end of study

Note that for post-baseline visits the date of visit is to be calculated from the previous visit date.

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated. Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be 4 for any summary statistic.

Categorical data will be summarized in terms of frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays. Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. The denominator for percentages will be further specified in this SAP. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

P-values greater than or equal to 0.001, in general, will be presented to 3 decimal places. P-values less than 0.001 will be presented as "<0.001". Confidence intervals (CIs) will be presented to one more decimal place than the raw data.

All missing or partial data will be presented in the participant data listing as they are recorded on the electronic case report form (eCRF). Endpoint-specific strategies for handling missing data in summaries will be discussed in the relevant section of this SAP.

5.2 Participant Dispositions

An overview of participant disposition will be provided for all ARASEC participants who signed informed consent, as well as the ARASEC ME-FAS and M-FAS, including the number enrolled, the number of screen failures, the number and percentage of participants who were assigned a treatment, who were treated, who were never treated, who are ongoing study treatment, who discontinued study treatment, who ended active follow-up, and who ended survival follow-up. Percentages will be based on the number of treated participants in each analysis set.

Note that screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study.

A summary of participant disposition during the treatment period will be presented for enrolled participants in the ARASEC cohort, the ARASEC ME-FAS and the M-FAS showing the number and percentage of participants never treated, who started treatment, who completed treatment, who terminated treatment along with reason for termination, and who are ongoing treatment. Percentages will be based on the number of participants in the analysis set.

A by-participant listing of disposition will also be presented for all ARASEC participants who signed informed consent, including: the participant identifier, age, race, ARASEC M-FAS flag, date of end of screening, date of enrollment, treatment start date, treatment end date, period, status (completed/ discontinued/ ongoing) for each period, date of discontinuation from study period (screening/ treatment/ active follow-up/ survival follow-up), and reason for discontinuation from each period.

A by-participant listing of participants who did not complete or pass screening will be presented for all ARASEC participants who signed informed consent, including the participant identifier, age, race, date of last visit, and reason for screening failure (criterion, which was not met, with description).

Informed consent information will be listed for all ARASEC participants who gave informed consent, including: the participant identifier, age, race, ARASEC M-FAS flag, protocol amendment number, informed consent date, and date of withdrawal of informed consent (if applicable).

5.3 Primary Endpoint(s) Analysis

5.3.1 Definition of Endpoint(s)

The primary endpoint is PFS in months. PFS is defined as the time interval from enrollment to PSA progression, clinical progression or death, whichever occurs first.

Clinical progression is defined as increasing symptomatic bone metastases, radiographic progression per RECIST criteria (v. 1.1) for soft tissue metastases and PCWG3 criteria for bone metastases, or clinical deterioration due to cancer per investigator's opinion.

PSA progression is defined as when the PSA demonstrates an increase that is more than 50% of nadir, taking as reference the lowest recorded PSA level since starting ADT. Two consecutive increases must be documented with each measurement obtained at least two weeks apart. Further details can be found in section 3 of the protocol.

Censoring and event assessments for PFS, consistent with CHAARTED are provided below:

Table 5–1 Censoring rules for time to progression free survival

Situation	End Date	Censored
PFS due to any of three components	The earliest event date among the three components of PSA progression, clinical progression (or sub-components) or death.	No
No baseline or post-baseline event assessment for all three components	Date of enrollment for ARASEC and randomization date for CHAARTED	Yes
Participant who died without documented progression with the Death occurring more than 3 months after the date of last disease assessment.	Date of the last PSA assessment before the consecutive missing PSA assessments or date of last radiological assessment, whichever comes later	Yes

Duration of time to event is defined as follows:

- If event/censoring date > enrollment date, then TTE (month) = (event/censoring date – enrollment date) / 30.44
- If event/censoring date = enrollment date, then TTE = 1 day = 0.033 month.

The date of clinical progression and date of PSA progression will be taken as documented on the eCRF. Note that the date of enrollment for the ARASEC cohort is defined as the date investigator confirms the participant meets all inclusion and exclusion criteria, and the equivalent date from the CHAARTED cohort is considered to be the date of randomization from the CHAARTED study.

5.3.2 Main Analytical Approach

In order to compare the ARASEC cohort participants who took darolutamide + ADT to participants who took ADT alone, the ARASEC participants will be matched in a 1:1 ratio with participants from the CHAARTED cohort via a propensity score-based caliper matching algorithm, as described in Section 6.1. The follow-up times for the matched CHAARTED participants will then be truncated according to Section 6.2. The primary analysis will be conducted when the 161 PFS event threshold for this analysis is reached. This is expected at about 12 months after the completion of enrollment.

Descriptive statistics of the baseline factors before and after the matching will be presented for the M-FAS and ME-FAS, including the number and percentage for categorical factors, the n/mean/SD/median/min/max for continuous factors, and the standardized mean difference

(SMD) for all baseline factors (as defined in Section 6.1). Additionally, side-by-side bar plots (histograms) comparing the propensity score distribution between cohorts before and after matching will be presented for the M-FAS and the ME-FAS, with the predicted probability on the x-axis and the frequency on the y-axis.

These descriptive statistics and bar plots will also be provided for the half-way matching exercise (after approximately half the participants are enrolled).

PFS (in months) will be summarized using the Kaplan Meier (KM) method for the M-FAS by treatment group. The number and percentage of events and censors, the 25th percentile, median, and 75th percentile of time to progression with 95% CIs, the range of survival times (both including and without censored values), and the survival rate at month 12, 18 and 24 with 95% CIs and the difference between in rates at month 12, 18 and 24 between the cohorts with 95% CI will be presented. CIs will be calculated via the Greenwood method. Percentages will be based on the number of participants in the M-FAS per treatment group. A Kaplan Meier plot of the time to progression will also be presented for each cohort, along with the number at risk.

Further, for the M-FAS the unstratified hazard ratio comparing the time to progression of the ARASEC cohort to the CHAARTED cohort will be estimated from a Cox proportional hazards (PH) model, along with 95% CI and p-value. Tied event times will be handled using the Breslow method, and the Cox model will include the effect of treatment only. The validity of the PH assumption will be assessed via a log-cumulative hazard plot (a plot of log time against the log of the cumulative hazard, which should show straight parallel lines to indicate that the PH assumption has been met) for the M-FAS.

Primary efficacy data will be listed for the M-FAS (for both ARASEC and CHAARTED cohorts), including: the participant identifier, study, treatment group, age, race, the PFS status (event/censored) and time to progression.

Soft tissue tumor assessment results will be listed for the ARASEC ME-FAS. For soft tissue target lesions, non-target lesions, and new lesions, the following will be included: participant identifier, age, race, visit, study day of assessment, method of assessment, tumor status (along with reason if not assessed), lesion number, anatomical location, anatomical description, and for target lesions only the longest diameter (mm), short axis (mm), and reason for non-measurement. Any variables not applicable to target, non-target or new lesions per the eCRF will be left blank or not included.

Calculations for soft tissue target lesions will also be listed for the ARASEC ME-FAS, including: the participant identifier, age, race, visit, study day of assessment, Sum of diameters of all target lesions (Longest diameter for non-nodal target lesions and short-axis for nodal target lesions) (mm), percentage change from baseline in sum of diameters, percentage increase from nadir in sum of diameters, absolute increase from nadir in sum of diameters (mm).

For bone lesions and new bone lesions, lesion assessment data will be listed for the ARASEC ME-FAS, including participant identifier, age, race, visit, study day of assessment, method of assessment, tumor status, total number of bone lesions, lesion number, anatomical location,

sub-location, and number of bone lesions at location. Any variables not applicable to either bone lesions or new bone lesions per the eCRF will be left blank or not included.

Serum PSA will also be listed, including: the participant identifier, age, race, date and time of collection, PSA total and unit.

Testosterone measurements will also be listed, including: the participant identifier, age, race, date and time of collection, testosterone level (ng/dL).

5.3.3 Sensitivity Analyses

Analyses of the primary endpoint will also be conducted using alternate methods to achieve balance between groups using propensity score based inverse weighting for all ME-FAS participants. This will entail using SAS PROC PHREG with a WEIGHT statement. Additionally, a Cox Regression model incorporating select covariates will be conducted as sensitivity analyses for the M-FAS, should some covariates have a standardized mean difference post-matching larger than 0.1. Analyses for the primary endpoint will also be conducted based on propensity scores (IPTW) and propensity matched cohorts obtained after treating missing Gleason score as an additional category instead of excluding these participants.

5.3.4 Supplementary Analyses

Not applicable.

5.4 Secondary Endpoint(s) Analysis

5.4.1 Key/Confirmatory Secondary Endpoint(s)

5.4.1.1 Definition of Endpoint(s)

The secondary efficacy endpoints for this study are as follows:

1. OS (in months), which is defined as time from the date of enrollment until death resulting from any cause. The date last known alive will be considered as censoring date.

Table 5–2 Censoring rules for OS

Situation	End Date	Censored
Documented death during study before or at data cut-off date	Death date	No
No documented death with no contacts after randomization and before or at data cut-off date	Date of randomization (Day 1)	Yes
No documented death before or at data cut-off date	Last known alive date (LKAD) or at the data 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 used as the LKAD by participant. Information from selected data, i.e. visit dates, exposure information, laboratory measurements, tumor assessment dates, demographics, survival status date, vital signs and disposition events or active or survival follow up assessments will be used to determine survival status.

2. rPFS (in months), which is defined as the time from enrollment to investigator-assessed radiographic progression per RECIST criteria (v. 1.1) for soft tissue metastases and PCWG3 criteria for bone metastases or death, whichever occurs first.

Censoring for rPFS is defined as follows:

Table 5–3 Censoring rules for time to radiological progression free survival

Situation	End Date	Censored
rPFS due to any of three components	The earliest event date among the three components of soft tissue metastases, bone metastases or death.	No
No baseline or post-baseline event assessment for all three components	Date of enrollment for ARASEC and randomization date for CHAARTED	Yes
Participant who died without documented progression with the Death occurring more than 3 months after the date of last disease assessment.	Date of last soft tissue or bone assessment, whichever comes later	Yes

3. Time to CRPC (in months), which is defined as the time from enrollment until documented clinical or PSA progression with a testosterone level of less than 50 ng per deciliter or documented medical castration or surgical castration. Censoring rules follow:

Table 5–4 Censoring rules for castration resistant prostate cancer

Situation	End Date	Censored
CRPC due to any of two components.	The earliest event date among the two components of PSA progression or clinical progression (including sub-components).	No
No baseline or post-baseline event assessment for all three components.	Date of enrollment for ARASEC and randomization date for CHAARTED	Yes
Participants without CRPC	Date of the last PSA assessment or date of last assessment for clinical progression, whichever comes later.	Yes

4. Complete PSA response rate at 6 months, 1 year, and at any time from enrollment date, where a PSA response is defined as a PSA level of less than 0.2 ng per milliliter on two consecutive measurements at least 4 weeks apart. Participants not meeting these criteria, or who have missing data, will be considered non-responders.

5. PSA30 response (the proportion of participants achieving ≥30% decrease in PSA from baseline after 6 months), PSA50 response (the proportion of participants achieving ≥50% decrease in PSA from baseline after 6 months) and PSA90 response (the

proportion of participants achieving ≥90% decrease in PSA from baseline after 6 months). Participants with missing data will be considered non-responders.

All time to event endpoints will be analyzed as described for the primary endpoint.

5.4.1.2 Main Analytical Approach

The analysis of the time to CRPC and Complete PSA response will be assessed using the primary analysis data cut. The time to CRPC analysis will involve truncation of the follow-up in the matched control cohort as described in Section 6.2.

The analysis for the rPFS endpoint is expected to occur after about 24 months after the end of enrollment when at least 137 rPFS are observed across cohorts. The tally of rPFS events as the study progresses will be done using a truncation of the follow-up in the CHAARTED control to that in the ARASEC cohort using a simpler algorithm which will consider only control events and censors occurring before the largest duration of time to rPFS events or censors in the ARASEC cohort. This algorithm will also be used to truncate follow-up for the OS endpoint in the control using the largest duration to event or censor in the ARASEC cohort. The differing truncation rule is justified as the asymmetry in follow-ups across the matched cohorts will be less marked than those for the PFS endpoint.
5.3.2

For the complete PSA response rate and PSA30/50/90 response, the number and percentage of participants with a response and a non-response, as well as the response rate (number of responders divided by number of participants) will be presented by treatment group for the M-FAS. The ARASEC and CHAARTED matched cohorts will be compared via a Fisher's exact test. The test statistic and p-value will be presented.

A by-participant listing of secondary efficacy data will also be presented for the M-FAS (for both the ARASEC and CHAARTED cohorts), including: the participant identifier, study, treatment group, age, race, the OS status (event/censored) and time to event, rPFS status and time to event, CRPC status and time to event, the complete PSA response status (responder/non-responder), and the relative PSA response (30%, 50% or 90%).

5.4.1.3 Sensitivity Analyses

As for the primary endpoint, analyses for the secondary endpoints will be conducted using alternate methods to achieve balance between groups using propensity score based inverse weighting. This will entail using SAS PROC PHREG with a WEIGHT statement. Analyses will also be conducted based on propensity scores (IPTW) and propensity matched cohorts obtained after treating missing Gleason score as an additional category instead of excluding these participants.

5.4.1.4 Supplementary Analyses

Not applicable.

5.4.2 Supportive Secondary Endpoint(s)

Not applicable.

5.5 Tertiary/Exploratory Endpoint(s) Analysis

Not applicable.

5.6 (Other) Safety Analyses

5.6.1 Extent of Exposure

Study drug is defined as darolutamide. 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, trailing "drug interruptions" will not be used in statistical tables. Interruption becoming permanent study treatment discontinuation is not accounted as an interruption.

Descriptive statistical summaries will be provided for the ARASEC ME-FAS and ARASEC M-FAS for the following variables:

- Overall time under treatment (or treatment duration), including time off drug and dose interruptions. It 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.
- Actual dose per day. Actual dose per day = total amount of dose / number of days with intake > 0.
- Total amount of dose. Total amount of dose = sum of dose received over total time under treatment.
- Percent of planned dose received. Percent of planned dose received = 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.

Dose modifications will be summarized for the ARASEC M-FAS and ARASEC ME-FAS analysis sets. The number and percentage will be presented for the following, with percentages based on the analysis set:

- Participants with any dose modification
- Participants with a dose reduction
- Participants with 1, 2, 3, etc. reductions
- Total number of dose reductions
- Reason for dose reduction
- Participants with a dose interruption
- Participants with 1, 2, 3, etc. interruptions
- Total number of interruptions
- Reason for interruption
- Participants with dose re-escalations

- Participants with 1, 2, 3, etc. re-escalations
- Total number of re-escalations
- Reason for re-escalation.

A by-participant listing of treatment exposure will be presented for the ARASEC ME-FAS, including: the participant identifier, age, race, ARASEC M-FAS flag, date of first exposure to treatment, date of last exposure to treatment, duration of exposure (days), duration of treatment (days).

A by-participant and visit listing of dosing information will also be presented for the ARASEC ME-FAS, including: the participant identifier, age, race, ARASEC M-FAS flag, visit, dose start date, dose end date, amount of study drug dosed (mg), route of administration, frequency, formulation, dose modification, and reason for dose modifications.

5.6.2 Adverse Events

Adverse events will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version at the time of database lock. All adverse event summaries will be performed on the ARASEC ME-FAS and ARASEC M-FAS. All analyses of AEs will be based on the number of participants with AEs, not on the number of AEs, unless otherwise stated. For reporting purposes, AEs will be divided into the following 2 categories:

- Pre-Treatment AEs: those that occurred prior to the start of study treatment
- Treatment-Emergent AEs (TEAEs): those that occurred or worsened in intensity after the start date/time of the first dose of darolutamide until 30 days after the last dose of darolutamide. AEs that worsened in intensity will be identified as those where the NCI CTCAE grade increases after the start date/time of the first dose of study treatment.

Analyses of AEs will be limited to treatment-emergent AEs, unless otherwise stated. Listings will include all AEs, and will indicate whether the AE is pre-treatment or treatment emergent. Missing or incomplete AE start and end dates will be imputed according to the rules specified in Section 6.11. The listings will present original (non-imputed) dates, if applicable.

For each participant and each adverse event, the worst severity (as recorded by NCI CTCAE grade version 5.0) recorded will be attributed and used in summaries of severity. Similarly, the worst causality (most related to treatment) will be attributed and used in summaries of causality. If severity or causality is missing, a conservative approach for AE assessment (taking the worst case into account) will be followed.

An overall summary of adverse events for the ARASEC ME-FAS and ARASEC M-FAS will present the number and percentage of participants with:

- TEAEs
- TEAEs by worst CTCTAE grade
- Serious TEAEs, including a breakdown of the type (congenital anomaly or birth defect/disability or permanent damage/death/ hospitalization (initial or prolonged)/life threatening/other serious (important medical events))

- TEAEs leading to discontinuation of treatment
- TEAEs with CTCAE grade ≥ 3
- TEAEs related to protocol related procedure
- TEAEs related to study drug
- TEAEs leading to dose modification (defined as either interruption, reduction or withdrawal of treatment)
- TEAEs leading to discontinuation of study
- Any AE leading to death.

Percentages will be based on the number of participants in the analysis set.

The number and percentage of participants with the following adverse event types will be summarized by primary system organ class (SOC) and preferred term (PT) for the ARASEC ME-FAS and ARASEC M-FAS except some by PT alone noted below:

- TEAEs
- TEAE's by age groups as in Section 5.7.2.
- Most common TEAEs (≥5% of participants)
- Most common TEAEs (≥5% of participants) - by PTs alone (without the SOC) in descending order
- TEAEs related to protocol required procedure
- TEAEs related to study drug
- TEAEs related to study drug by age groups as in Section 5.7.2.
- Most common study drug related TEAEs (≥5% of participants) - by PTs alone (without the SOC) in descending order
- Treatment emergent SAEs
- Treatment emergent SAEs by age group as in Section 5.7.2.
- Treatment emergent SAEs related to study drugTreatment emergent SAEs leading to discontinuation of study
- Most common treatment emergent SAEs (≥5% of participants)
- Most common treatment emergent SAEs (≥5% of participants) - by PTs alone (without the SOC) in descending order
- TEAEs leading to discontinuation of study
- TEAEs leading to discontinuation of study and related to study drug
- TEAEs of CTCAE grade ≥3
- Most common TEAEs of CTCAE grade ≥3 (≥5% of participants)
- AEs with outcome of death
- AEs with outcome of death related to study drug
- Pre-treatment AEs.

The number and percentage of participants with the following adverse event types will be summarized by SOC, PT and maximum CTCAE grade for the ARASEC ME-FAS and ARASEC M-FAS:

- TEAEs
- Pre-treatment AEs

- Treatment emergent SAEs
- TEAEs leading to discontinuation of study.
- TEAEs related to study drug

Analysis of Special Topics, as defined for the mHSPC darolutamide ARANOTE study, will be provided for TEAEs, SAEs and Drug related TEAEs.

The number and percentage of participants with the following adverse event types will be summarized by SOC, PT and worst outcome (Unknown/ Recovered/resolved/ Recovering/resolving/ Recovered/resolved with sequelae / Not recovered/not resolved /Fatal) for the ARASEC ME-FAS and ARASEC M-FAS:

- TEAEs
- Treatment emergent SAEs
- TEAEs leading to discontinuation of study.
- TEAEs related to study drug

For the following AE types, the total number of AEs and the event rate per 100 person-years (derived as the number of events divided by [total treatment duration in years / 100]) will be presented by SOC and PT for the ARASEC ME-FAS and ARASEC M-FAS:

- TEAEs
- Treatment emergent SAEs.
- TEAEs related to study drug

Percentages will be based on the number of participants in the analysis set. Participants with multiple AEs within the same SOC and/or PT, CTCAE grade, and outcome are counted once per SOC and PT, grade and outcome, as applicable. The SOCs and PTs will be sorted alphabetically.

A by-participant listing of all adverse events will be presented for the ARASEC ME-FAS. This listing will include: participant identifier, age, race, ARASEC M-FAS flag, period of AE (pre-treatment/ treatment-emergent), SOC, PT, AE verbatim term, seriousness, type of serious AE, start date, end date, duration of AE (days), AE start and end relative day, CTCAE grade, relation to study drug, relation to protocol required procedure, action taken, outcome, whether remedial therapy was required. This listing will be repeated for AEs leading to discontinuation of study and serious AEs.

A listing of deaths during treatment and within 30 days post permanent treatment discontinuation will be presented for the ARASEC ME-FAS, including: the participant identifier, age, race, ARASEC M-FAS flag, last dose of medication and unit, treatment start and stop dates and number of months on treatment, date of death, relative day of death to start and stop of treatment, the primary cause of death, and SOC. PT and verbatim term of the associated adverse event. This listing will be repeated for deaths after 30 days post treatment discontinuation, excluding the SOC, PT and verbatim term. It will also be repeated for deaths occurring before treatment, excluding the SOC, PT and verbatim term, treatment start and stop dates and number of months on treatment, and relative day of death to start and stop of treatment.

A listing of SOC, PT and verbatim terms reported in the study will also be provided.

5.6.3 Clinical Laboratory Evaluation

The analyses of laboratory data will be descriptive in nature, and will be done on the ARASEC ME-FAS and ARASEC M-FAS. All analyses will be based on SI units and on standardized values. Results from the local laboratories will be included in the reporting of this study for the following laboratory groups:

- Chemistry
- Hematology
- Coagulation
- Urinalysis.

Protocol required laboratory assessments for hematology and chemistry can be found in Appendix 6.12.

At each visit, laboratory measurements will be compared with the relevant laboratory reference ranges and categorized as abnormal (low/high) or normal as follows:

- Low: below the lower limit of the laboratory reference range
- Normal: within the laboratory reference range (upper and lower limit included)
- High: above the upper limit of the laboratory reference range.

For chemistry and hematology, summaries of the number and percentage of participants' worst CTCAE grade (according to CTCAE 5.0) before start of treatment and after the start of treatment will be provided by event category and NCI CTCAE term as well as a shift table of the grade from last value before the start of treatment to worst value after the start of treatment by parameter. Denominators for percentages for each laboratory value will be the number of participants with the specific lab value available. If the reference ranges or other information necessary to derive grades are unavailable or result has a special character (such as > or <) then the grade is set to "not graded". In the event of overlapping CTCAE criteria ranges for specific laboratory tests, the higher grade should be assigned. The following laboratory tests will be included in these summaries:

- Hematology:
  - Hemoglobin
  - White blood cell count
  - Neutrophils
  - Platelet count
- Chemistry:
  - Alkaline phosphatase
  - Aspartate aminotransferase
  - Alanine aminotransferase
  - Bilirubin
  - Glucose
  - Creatinine

- Gamma-glutamyl Transferase (GGT).

For by-visit summaries, the last non-missing assessment (including repeat assessments) recorded at each visit will be summarized, and unscheduled visits will not be included. For across-visit summaries, scheduled, unscheduled and repeated assessments will be included. Tabular summaries will present results from visits during the treatment period. Listings will present all visits, including unscheduled ones.

Chemistry and hematology laboratory values will be listed by participant and study time point including: the participant identifier, treatment group, age, race, ARASEC M-FAS flag, visit, specimen collection date and time, laboratory parameter and unit, result, change from baseline, CTCAE grade, flag (low/normal/high), clinical significance, normal range lower limit, and normal range upper limit, whether participant was fasting, specimen condition if not normal. Coagulation and urinalysis laboratory values will also be listed including the same variables, except whether participant was fasting and specimen condition if not normal. For the urinalysis listing, method of examination will also be presented.

5.6.4 Vital Signs

The following vital signs parameters will be assessed:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Heart Rate (beats/min)
- Temperature (degrees Celsius).

A by-participant listing of vital sign parameters will be presented for the ARASEC ME-FAS, including participant identifier, age, race, ARASEC M-FAS flag, visit, measurement date and time, vital sign parameter, unit, result and change from baseline.

5.6.5 Electrocardiogram

The following electrocardiogram (ECG) parameters will be assessed:

- Ventricular rate (beats/min)
- Mean PR interval (msec)
- Mean QRS interval (msec)
- Mean QT interval (msec)
- QTcF - Fridericia's Correction Formula (msec)
- Atrial fibrillation (yes/no).

For by-visit summaries, the last non-missing assessment (including repeat assessments) recorded at each visit will be summarized, and unscheduled visits will not be included. For across-visit summaries, scheduled, unscheduled and repeated assessments will be included. Listings will present all visits, including unscheduled ones.

A summary of the percentage of abnormal ECG findings over time (normal/ abnormal – not clinically significant/ abnormal – clinically significant) will be presented for the ARASEC ME-FAS and ARASEC M-FAS by visit. The number and percentage of participants with abnormalities will be presented at each visit, with percentages based on the analysis set.

A by-participant and visit listing of ECG information will also be presented for the ARASEC ME-FAS, including: the participant identifier, age, race, ARASEC M-FAS flag, parameter, visit, date and time of measurement, repetition number, result, unit, and interpretation (normal/ abnormal – not clinically significant/ normal – clinically significant) for all collected ECG parameters.

5.6.6 Echocardiogram

A left ventricular fraction ejection from the echocardiogram scan will be assessed at baseline. The results will be listed for the ARASEC ME-FAS including: the participant identifier, ARASEC M-FAS flag, visit, date and time of assessment, test parameter and unit, result, and interpretation of result (normal/ abnormal – not clinically significant/ abnormal – clinically significant).

5.6.7 Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status will be summarized descriptively. The ECOG performance status is described via the grades in the table below

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

A shift table of the baseline to post-baseline ECOG performance status by visit will be presented for the ARASEC ME-FAS and ARASEC M-FAS. The number and percentage of participants will be presented for each shift combination, and percentages will be based on the total number of participants with each ECOG performance status at baseline per analysis set.

ECOG performance status will also be listed for the ARASEC ME-FAS, including: the participant identifier, age, race, ARASEC M-FAS flag, visit, date of measurement, and ECOG performance status.

5.7 Other Analyses

5.7.1 Other Variables and/or Parameters

For testosterone at the treatment phase visits for the ARASEC ME-FAS and ARASEC M-FAS, the differences between the log transformed data at the visit and that at baseline will be estimated with 95% CI using SAS PROC MIXED with the ESTIMATE statement. The mean and 95% CI of the differences between week 12 and baseline values will be computed and back transformed by exponentiation to obtain the mean fold change M_F with its 95% CI [L_F, U_F]. The mean percent change Δ can be obtained as $\Delta = 100*(M_F-1)$ with CI [$100*(L_F-1)$, $100*(U_F-1)$]. In addition to the estimated mean percent change and its CI, summary statistics will include the mean fold change with CIs, and the range, minimum, maximum and quartiles of percent change computed from the raw Week 12 and baseline testosterone values.

5.7.2 Subgroup Analyses

As an exploratory analysis, subgroup analyses for the primary endpoint (PFS) will be provided for the baseline factors identified in Section 6.1:

- Age (<70 vs ≥70 years)
- ECOG Performance Status (0 vs >0)
- Extent of disease
  - High volume with Visceral metastasis
  - High volume with Bone metastasis only (no Visceral metastasis)
  - Low volume
- Prior Local Therapy (Yes vs No; as proxy for Recurrent vs. De-novo mHSPC)
- Gleason Score (<8 vs ≥8)
- PSA category [ng/mL] (<= 10 vs >10)

Low volume disease is defined as any metastatic disease that is not high volume disease. High volume disease is defined as:

- Visceral Metastases (extranodal). This can be identified from ‘Non-regional lymph node metastasis’ or ‘Visceral metastases with or without lymph node metastases with or without bone metastases’ fields on the ‘Prostate Cancer Classification’ eCRF page. This should be compared to the presence of non-lymph nodal lesions recorded on the ‘Soft Tissue Target Lesions PCWG3’ and ‘Soft Tissue Non-Target Lesions PCWG3’ eCRF forms to confirm.
  AND/OR
- Bone Metastases with at least 4 or more bone lesions, one of which must be outside of the vertebral column AND pelvis. This can be identified from the ‘Bone metastasis with or without lymph node metastases’ field on the ‘Prostate Cancer Classification’ eCRF page and confirmed with the number and location of bone lesions on the ‘Bone Lesions PCWG3’ eCRF form.

High volume disease with visceral metastasis can be identified as high volume disease per the definition above, with non-lymph nodal lesions that can be identified on the 'Soft Tissue Target Lesions PCWG3' and 'Soft Tissue NonTarget Lesions PCWG3' eCRF forms

High volume disease with bone metastasis only (no Visceral metastasis) can be identified as high volume disease per the definition above, with at least 4 or more bone lesions, one of which must be outside of the vertebral column AND pelvis, which can be identified from the 'Bone Lesions PCWG3' eCRF form. Additionally, there must be no non-lymph nodal lesions (visceral metastasis) that can be identified on the 'Soft Tissue Target Lesions PCWG3' and 'Soft Tissue NonTarget Lesions PCWG3' eCRF forms

The above identifications of high/low volume disease should be reviewed by the Medical Monitor to confirm whether the disease is high volume or low volume, and whether the high volume disease is with visceral or bone metastases.

Subgroup analyses for bone metastases and visceral metastases will be presented for those with bone metastases alone and for visceral metastases with or without bone, amongst those with high-volume disease as was collected for CHAARTED. Other factors considered relevant and prognostic of the outcome may also be considered before SAP finalization, when classifications based on these are of adequate size.

A forest plot of the hazard ratio for the matched ARASEC versus the matched CHAARTED cohorts in the M-FAS along with 95% CIs will be presented with all subgroups on the same plot. The number and percentage of events in each subgroup (with percentages based on the M-FAS) will also be displayed on the plot. The hazard ratio will be unstratified and will use the Breslow method to handle tied event times. The treatment, subgroup variable and the treatment by subgroup interaction will be included in the Cox model. Participants with missing values of the subgroup variables will be excluded from the analysis.

5.8 Interim Analyses

No interim analysis requiring additional control of the false positive rate will be conducted.

A matching exercise will be conducted part-way through enrollment to gauge actual matching rates in order to consider increases in enrollment in the event of a projected short-fall. No post-baseline outcome or dosing data will be shared with the Matching analysts at this time. The matching exercise will be done after about half the participants are enrolled. The final matching and analyses at the two data cuts will be conducted as described in Section 1.

5.8.1 Data Monitoring Committee or Other Review Board

There will be no Data Monitoring Committee for this study.

6. Supporting Documentation

6.1 Appendix 1: Propensity Score Matching

The following describes the propensity score-based caliper matching algorithm that will be used to achieve 1:1 matching between the ARASEC cohort participants who took darolutamide + ADT to the CHAARTED participants who took ADT alone. The results of this matching will form the M-FAS as described in Section 4 and will be used for the primary and secondary efficacy analyses. The matching will be conducted by analysts who are blinded to the post-baseline efficacy outcome data of the ARASEC study.

The matching algorithm will be based on propensity scores such that each participant in the ARASEC cohort is matched with one participant from the CHAARTED cohort that has a similar value of the propensity score, subject to a specified caliper width. In subsequent analysis, the treatment effect of darolutamide + ADT compared to ADT alone can be estimated by comparing outcomes between ARASEC and CHAARTED participants in the matched sample.

Matching will be conducted using the following baseline factors which are likely to affect the primary outcome and are available in Datasphere for the CHAARTED study:

- Age (<70 vs ≥70 years)
- ECOG Performance Status (0 vs >0)
- Extent of disease
  - High volume with Visceral metastasis
  - High volume with Bone metastasis only (no Visceral metastasis)
  - Low volume
- Prior Local Therapy (Yes vs No; as proxy for Recurrent vs. De-novo mHSPC)
- Gleason Score (<8 vs >=8) [non-missing data across cohorts]
- PSA category [ng/mL] (<= 10 vs >10)

It is noted that given the CHAARTED data format, the extent of disease items will be analyzed as a three factor variable with levels shown above. The matching algorithm is described below, and can be performed using the PSMACH procedure in SAS:

1. Compute the propensity scores for both ARASEC and CHAARTED participants. The propensity score is defined as p(T=1|X), which is the probability of a participant being assigned to darolutamide + ADT treatment given the set of covariates X. The propensity score can be computed via a logistic regression model

$$\log\left(\frac{p(T=1|X)}{1-\ p(T=1|X)}\right) = \ \beta 0 + \ \beta 1 X 1 + \cdots$$

   Where β are coefficients and X are the covariate values.

2. Match the ARASEC participants to the CHAARTED participants on the propensity score. The greedy nearest neighbor method without replacement will be implemented

(1 matching CHAARTED participant for each ARASEC participant). A caliper will also be used such that that the difference in the propensity scores for a matched pair must be less than or equal to a specified caliper width. The caliper will initially be set to 0.20 times the pooled estimate of the common standard deviation of the logit of the propensity scores (where this estimate is computed as the square root of the average of the variances in the ARASEC and CHAARTED cohorts), and caliper values of 0.1 and 0.05 may be considered.

3. Assess the covariate balance in the matched sample between the ARASEC and CHAARTED participants. Covariate balance will be assessed via SMDs. For continuous factors, the SMD is calculated as (Zhang et al. 2019)

$$SMD = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{(S_1^2 + S_2^2)/2}}$$

Where $\bar{X}_1$ and $\bar{X}_2$ are sample mean for the ARASEC and CHAARTED matched cohorts, respectively, and S_1^2 and S_2^2 are sample variance for the ARASEC and CHAARTED matched cohorts.

For categorical factors with K levels, the SMD is calculated as (Yang and Dalton 2012)

$$SMD = \sqrt{(T - C)' S^{-1} (T - C)}$$

Where S is a $(k-1) \times (k-1)$ covariance matrix defined as

$$S = [S_k] \begin{cases} \frac{[\hat{P}_{1k}(1 - \hat{P}_{1k}) + \hat{P}_{2k}(1 - \hat{P}_{2k})]}{2}, k = l \\ -\frac{[\hat{P}_{1k}\hat{P}_{1l} + \hat{P}_{2k}\hat{P}_{2l}]}{2}, k \neq l \end{cases}$$

And T and C are vectors

$$T = (\hat{P}_{12}, \hat{P}_{13}, \dots, \hat{P}_{1k})'$$
$$C = (\hat{P}_{22}, \hat{P}_{23}, \dots, \hat{P}_{2k})'$$

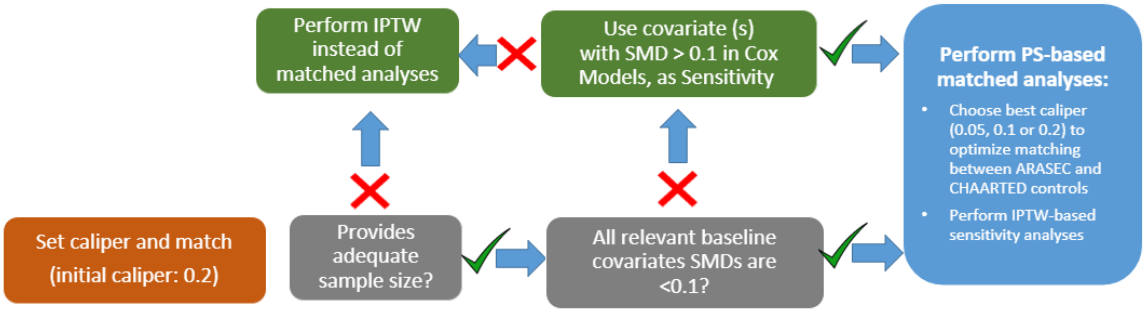
Where $\hat{P}_{jk} = \Pr(\text{category } k | \text{ treatment group } j), j \in \{1,2\}$ and $k \in \{2,3, \dots, K\}$.

For both the categorical and continuous SMD calculations, for critical factors, a SMD of >0.1 would indicate an imbalance between the groups for that particular factor (Zhang et al. 2019) for core baseline characteristics. For other factors, a SMD of 0.2 will be used.

4. If the balance is considered good enough per the step above, then the final matched cohort has been identified, and the matching process will stop. When SMD >0.1, the baseline factor will be included in the outcome model as sensitivity analyses.

5. In the case that the balance is not acceptable, the above process may be repeated with a different set of baseline factors for the logistic regression model, a different set of matching criteria, or a different matching method.

The final set of matched participants will form the basis of the analysis populations described in Section 4.



IPTW: inverse probability of treatment weighting; PS: Propensity Score; SMD: Standardized Mean Difference

6.2 Appendix 2: Follow-Up Time Truncation

The expected study duration for the PFS endpoint is 27 months, assuming participants are enrolled approximately at a rate of 15 participants per month, and an enrollment ramp-up time of 3 months. An additional follow-up of one year is expected before the assessment of the rPFS endpoint. These durations are longer in the CHAARTED control, (Sweeney et al. 2015) where the accrual period for the study extended from July 2006 to December 2012, a period of 6.5 years. The Datasphere data contains data till 23rd April 2016 on the primary endpoint, yielding more than 3 years of potential follow-up data for the last participant enrolled. To provide a control cohort comparable to the ARASEC cohort at a cut-off point, we will obtain from the matched ARASEC cohort, the maximum potential follow-up time f for the last participant enrolled and the total accrual time a. Hence, all participant follow-ups would be distributed between f and $f + a$.

Participant-wise truncated follow-ups will be sampled using fixed pre-specified seeds from the ARASEC distribution of potential follow-ups and merged into the matched CHAARTED control data. We use the word 'potential' to denote follow-up's attainable irrespective of whether the participant was actually censored or had had an event before data cut-off. The duration of time to event or censoring in the available control data will be reassessed participant-wise using truncated follow-ups. When this follow-up is less than the time to event or censoring in the control data, this duration will be reduced to the truncated follow-up and the participant will be deemed censored.

The analytical argument is like that in the computation of expected events rates when computing the sample size in time-to-event trials, such as that in (Collett 2003). The expected follow-up is given by

$$\int_0^a (f + a - t).dF(t) = \int_f^{f+a} t.dF^*(t)$$

Where f and a are as noted before and $F(t)$ is the distribution of accrual times. This is equivalent to the expression using $F^*(t)$, the distribution of potential follow-up's induced in the range from f to $f + a$ through the accrual distribution. Under uniform accrual, this evaluates to $f + 0.5 * a$, half-way through the range. Due to the enrollment ramp-up time noted earlier and possible variation in planned enrollment rates, this expected follow-up may differ. Sampling from the distribution $F^*()$ for truncations to follow-up in the matched CHAARTED control, will carve out equivalent follow-up.

The process for truncation the follow-up for the CHAARTED matched control participants for Event Tracking and Analysis will be as follows:

Step 1a: For the matched ARASEC cohort post-matching, we compute the participant-wise follow-up or observation period for events A_PWFU as follows:

A_PWFU = {Calendar Date} - {Participant Treatment Start date}

This is the potential follow-up at calendar date irrespective of censoring or event. We would use the current calendar date for event tracking and the data-cut-off date for analysis.

Step 1b: Then we order A_PWFU from smallest to largest and associate with a sequence number.

Step 2: The estimated participant wise follow-up is not being provided by ECOG-ACRIN to maintain participant confidentiality. However, the year of enrollment has been provided. Steps 2 through 5 provide a censoring and event agnostic algorithm for truncating follow-up. For the CHAARTED matched participants compute follow-up for each participant C_LPIFP as:

C_LPIFP = {Apr 23 2016 cut-off Date} - { Enrollment Date = Dec 31 20XX}

Where 'XX' is the year of enrollment provided.

Step 3: Then compute the estimated minimal participant wise follow-up for the CHAARTED matched control C_EPWFU as:

C_EPWFU = Max {OS_Dur, C_LPIFP},

where OS_Dur is the max of the time to OS event or time known alive in CHAARTED (censored due to lost to follow-up or data cut-off) for the participant. Step 4 below involves random selection of ARASEC follow-ups for CHAARTED follow-up truncation to achieve a censor/event agnostic truncation of follow-up as specified in the protocol.

Step 4: Randomly re-order to CHAARTED participant Data using a fixed seed and associate with a sequence number. Call this data C_Random.

Step 5: Merge in the ARASEC ordered follow-up variable into the CHAARTED data by sequence number and compute the truncated CHAARTED follow-up C_TPWFU as:

C_TPWFU = MIN {A_PWFU, C_EPWFU}

Step 6: For CHAARTED time to event C_Ordered data compute truncated time to event/censoring T_Duration and the new Censor flag for event/censoring T_Censor as:

T_Duration = MIN {Duration, C_TPWFU},

If T_Duration = Duration, then T_Censor = Censor;
Else T_Censor = 1;

where Duration and Censor are the original participant time to event/censoring and the Censoring flag as reported in the CHAARTED study.

Step 7: Harmonize the differing variable names across the treated and control cohorts for duration and censor using values on truncation from the CHAARTED control.

For Event Tracking:
Tally Censor = 0 across the two matched datasets. Report blinded event totals to sponsor to assist in timing of the analyses (for PFS and rPFS). For PFS, the analysis will be performed when at least 161 PFS events occur (expected to occur after about 12 months of follow-up after last participant enrolls). For rPFS, at least 137 rPFS events need to occur before this endpoint is analyzed (expected to occur after about 24 months of follow-up).

For Analysis:
Compare matched cohorts using the harmonized time to event variables.

6.3 Appendix 3: Protocol Deviations

Important protocol deviations (PDs) are defined as those deviations from the protocol likely to have an impact on the participant's rights, safety, well-being, and/or validity of the data for analysis. Important PDs and any action to be taken regarding the exclusion of participants or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification.

A summary of the number and percentage of participants with an important protocol deviation by PD classification and PD term will be presented for all enrolled participants in the ARASEC cohort, the ARASEC ME-FAS, and the ARASEC M-FAS with percentages based on the number of participants in the analysis set.

A by-participant listing of important protocol deviations will also be presented for all enrolled participants in the ARASEC cohort, including the participant identifier, age, race, ARASEC M-FAS flag, trial unit, PD classification and PD term.

6.4 Appendix 4: Demographic and Baseline Characteristics and Disease History

Descriptive summaries of demographic and baseline characteristics will be presented for the ARASEC ME-FAS, ARASEC M-FAS, CHAARTED ME-FAS AND CHAARTED M-FAS.

Percentages will be based on the number of participants in the analysis set. The number of participants with missing values for categorical summaries may be presented if any such values are present in the data.

Summaries of the following demographic characteristics will be presented for the ARASEC ME-FAS AND ARASEC M-FAS:

- Age (years)
- Categorized age (<65, 65 to <75, ≥75 and <70, ≥70)
- Ethnicity (Not Hispanic or Latino/ Hispanic or Latino/ Not Reported)
- Sex (Male)
- Race (White/ Black or African American/ Asian/ American Indian or Alaska Native/ Native Hawaiian or other Pacific Islander / Not Reported/ Multiple) – note that participants who select multiple race groups on the eCRF will be summarized as 'multiple'
- Country
- Body mass index (BMI) (kg/m^2)
- Body mass index category (BMI) [kg/m^2] (< 20, 20 to 25, 25 to 30, ≥ 30, Missing)

Summaries of the following demographic characteristics will be presented for the CHAARTED ME-FAS AND CHAARTED M-FAS:

- Age (years)
- Categorized age (<65, 65 to <75, ≥75 and <70, ≥70)
- Sex (Male)
- Race (White/ Black/ Other/ Unknown)
- Country
- Body mass index (BMI) (kg/m^2)
- Body mass index category (BMI) [kg/m^2] (< 20, 20 to <25, 25 to <30, ≥ 30, Missing)

Body mass index will be calculated as [weight (kg) / [height (m)]^2].

Summaries of the following disease history information will be presented for the ARASEC ME-FAS and ARASEC M-FAS with percentages based on the analysis set:

- Time since initial diagnosis to start of study treatment (years)
- Time since first progression or relapse to start of study treatment (years)
- Time since most recent progression or relapse to start of study treatment (years)
- Baseline PSA (ng/mL)
- Baseline PSA category [ng/mL] (≤10, >10 to ≤20, >20)
- Gleason score category (Gleason ≤6, Gleason 3+4=7, Gleason 4+3=7, Gleason 8, Gleason 9 or 10, Gleason X)
- Gleason score category (<8, ≥8, or Gleason X)
- Time since diagnosis of metastases (years)

- 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) – note that the most advanced category is selected when there is more than one site of metastases per the eCRF
- Presence of low volume disease/ high volume disease (high volume with visceral metastasis, or high volume with bone metastasis only [no visceral metastasis])
- Baseline ECOG performance status (0/ 1/ 2/ 3/ 4)
- Baseline hemoglobin (g/dL)
- Baseline alkaline phosphatase (U/L)
- Baseline testosterone (nmol/L).

Summaries of the following disease history information will also be presented for the CHAARTED ME-FAS AND CHAARTED M-FAS with percentages based on the analysis set:

- Interval from randomization to date of PSA assessment at diagnosis (months)
- PSA at randomization (ng/mL)
- PSA at randomization category [ng/mL] (≤10, >10 to ≤20, >20)
- Gleason score (Gleason ranging 2-10)
- Gleason score category (Gleason ≤6, Gleason 3+4=7, Gleason 4+3=7, Gleason 8, Gleason 9 or 10)
- Gleason score category (<8 or ≥8)
- Presence of low volume disease/ high volume disease (high volume with visceral metastasis, or high volume with bone metastasis only [no visceral metastasis])
- Baseline ECOG performance status (0/ 1/ 2/ 3/ 4)
- Prior orchiectomy
- Prior radiation therapy
- Prior radiation therapy purpose type
- Prior or future use of bisphosphonates
- History of hypertension or hypertension present at baseline
- History of obesity or obesity present at baseline
- History of hypertriglyceridemia or hypertriglyceridemia present at baseline
- Receiving metformin at study entry and planning on being continued while on study

A summary of the number and percentage of participants with any visceral or soft tissue metastases will be presented for ARASEC ME-FAS, ARASEC M-FAS, CHAARTED ME-FAS AND CHAARTED M-FAS with percentages based on the number of participants in the analysis set. Anatomical location and anatomical location category will also be summarized by number and percentage for those mentioned analyses sets, with percentages based on the number of total participants with any visceral or soft tissue metastases.

Demographic and baseline characteristics will also be listed for the ARASEC ME-FAS, including the participant identifier, ARASEC M-FAS flag, year of birth, age (years), sex, ethnicity, race (including multiple races if multiple were selected on the eCRF), baseline height, baseline weight and BMI.

Prostate cancer classification information will be listed for the ARASEC ME-FAS, including: the participant identifier, age, race, ARASEC M-FAS flag, date of initial diagnosis and time since initial diagnosis to start of study treatment (years), date of first progression or relapse and time since first progression or relapse to start of study treatment (years), date of most recent progression or relapse and time since most recent progression or relapse to start of study treatment (years), staging system at initial diagnosis, AJCC grade/Gleason score category at initial diagnosis, staging system at study entry, date of metastases diagnosis and time since metastases diagnosis (years), extent of metastatic disease at study entry, residual primary tumor status, and presence of low volume/high volume disease, time since start of first prior antiandrogen to start of study treatment (months), baseline ECOG performance status, and baseline PSA.

6.5 Appendix 5: Medical History

Participant medical history will be presented for the ARASEC ME-FAS and the ARASEC M-FAS. The number and percentage of participants with medical history findings will be presented by SOC and high level term (HLT). Percentages will be based on the number of participants in the analysis set. Participants with multiple medical history findings within the same SOC/HLT will be counted once per SOC/HLT. The medical history findings will be sorted alphabetically by SOC and then HLT.

Additionally, the number and percentage of participants with medical history findings ongoing at study entry will be presented by SOC, PT and CTCAE grade at baseline for the ARASEC ME-FAS and the ARASEC M-FAS. Percentages will be based on the number of participants in the analysis set. Participants with multiple medical history findings within the same SOC/PT/CTCAE grade will be counted once per SOC/PT/grade. The medical history findings will be sorted alphabetically by SOC and then PT and then CTCAE grade.

A by-participant listing of medical history findings will also be presented for the ARASEC ME-FAS, including: the participant identifier, age, race, ARASEC M-FAS flag, SOC, HTL, PT, verbatim term, start date, end date, and an indication of whether the finding was ongoing at study entry, and the CTCAE grade at baseline (if finding ongoing at baseline).

Medical history conditions will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version at the time of database lock and graded according to CTCAE version 5.0.

6.6 Appendix 6: Prior and Concomitant Medications

Prior and concomitant medications will be coded according to the most recent available World Health Organization - Drug Dictionary (WHO-DD) version.

ATC class is taken from ATC level 1, and ATC subclass is taken from ATC level 3.

A by-participant listing of all prior, concomitant and post-treatment medications will be presented for the ARASEC ME-FAS, including: the participant identifier, age, race, ARASEC M-FAS flag, ATC class, ATC subclass, reported name of medication, start relative to treatment (before/after), end relative to treatment (before/after), medication start date,

medication stop date, whether ongoing at last visit, main indication for medication. Original (non-imputed) start and end dates will be presented in the listing.

Medication start and stop dates will be compared to the date of first dose of study treatment to allow medications to be classified as either Prior only, both Prior and Concomitant, or Concomitant only. Medications starting after the completion/withdrawal date will be listed but will not be classified or summarized. Medications that start and stop prior to the date of first dose of study treatment will be classified as Prior only. If a medication starts before the date of first dose of study treatment and stops on or after the date of first dose of study treatment, then the medication will be classified as both Prior and Concomitant. Medications will be classified as Concomitant only if they have a start date on or after the date of first dose of study treatment.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study treatment. Medications will be assumed to be Concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the first dose of study treatment. If there is clear evidence to suggest that the medication started prior to the first dose of study treatment, the medication will be assumed to be both Prior and Concomitant, unless there is clear evidence to suggest that the medication stopped prior to the first dose of study treatment. If there is clear evidence to suggest that the medication stopped prior to the first dose of study treatment, the medication will be assumed to be Prior only. Concomitant medications with partial or incomplete start/stop dates will be assigned to all treatments for which there is no clear evidence to suggest the treatment was not applicable.

6.7 Appendix 7: Concomitant Androgen Deprivation Therapy

Concomitant androgen deprivation therapies will be coded according to the most recent available WHO-DD version.

The number and percentage of participants who received concomitant androgen deprivation therapy will be summarized type of medication (as recorded on the eCRF) and drug name for the ARASEC ME-FAS and the ARASEC M-FAS. Percentages will be based on the number of participants in the analysis set. Participants with multiple therapies will be counted once per therapy.

Concomitant androgen deprivation therapies will also be listed for the ARASEC ME-FAS, including: the participant identifier, age, race, ARASEC M-FAS flag, reported name of medication, type of medication, dose, unit, frequency, route, therapy start date, therapy stop date, and whether therapy was ongoing at participant's last visit.

6.8 Appendix 8: Prior and Concomitant Systemic Anti-Cancer Therapies

An overall summary of prior and subsequent systemic anti-cancer therapies will be provided for the ARASEC ME-FAS and the ARASEC M-FAS, including the number and percentage of participants with each treatment intent (palliative/ curative/ unknown) and regimen number. The number and percentage of participants who received systemic anti-cancer therapies will be presented for prior and subsequent systemic anti-cancer therapies.

The therapies will be classed as prior per the eCRF. The therapies will be classed as subsequent if they start after Darolutamide treatment has stopped per the date of therapy on the 'Concomitant Systemic Anti-Cancer Therapy' eCRF form. The therapies will be summarized by WHO-DD ATC class and subclass for the ARASEC ME-FAS, where ATC class is taken from ATC level 1, and ATC subclass is taken from ATC level 3. Percentages will be based on the number of participants in the analysis set. Participants with multiple therapies within the same ATC class and subclass will be counted only once per ATC class and subclass. The therapies will be sorted alphabetically by ATC class and subclass.

A by-participant listing of all prior systemic anti-cancer therapies will be presented for the ARASEC ME-FAS, including: the participant identifier, age, race, ARASEC M-FAS flag, ATC class, ATC subclass, reported name of therapy, start date, end date, regimen number, treatment intent, discontinuation reason for regimen, reason to move to next line of therapy and date of progression to regimen.

A by-participant listing of subsequent systemic anti-cancer therapies will be presented for the ARASEC ME-FAS, including: the participant identifier, age, race, ARASEC M-FAS flag, ATC class, ATC subclass, reported name of therapy, start date, end date, and regimen number.

A table of subsequent systemic life prolonging therapies will also be provided for the ARASEC ME-FAS and the ARASEC M-FAS. This will include the number and percentage of participants who received each type of systemic life prolonging therapy. Life prolonging therapies are defined as the following anti-cancer therapies: abiraterone, apalutamide, enzalutamide, docetaxel, cabazitaxel, radium-223, sipuleucel-T, and lutetium-177.

6.9 Appendix 9: Prior and Concomitant Surgical, Diagnostic and Therapeutic Procedures and Radiotherapy

Summaries of prior and concomitant local therapy will be provided for the ARASEC ME-FAS and the ARASEC M-FAS. Local therapy is defined as either radiotherapy or surgical procedures (prostatectomy/ other). The number and percentage of participants with any local therapy and with each type of therapy (prostatectomy/ other/ radiotherapy) will be provided, with percentages based on the analysis set.

Summaries of prior hormonal therapy and orchiectomy will be provided for the ARASEC ME-FAS and ARASEC M-FAS. The number and percentage of participants with at least one prior hormonal therapy or orchiectomy and with each type of therapy (LHRH agonist/antagonist only/ orchiectomy only/ LHRH agonist/antagonist and orchiectomy) will be provided, with percentages based on the analysis set.

Post-treatment surgical, diagnostic and therapeutic procedures and radiotherapy will be classed as prior or concomitant according to the eCRF. LHRH agonist/antagonist therapy will be classed as prior if the therapy was started prior to the first dose of study treatment.

Prior, concomitant and post-treatment surgical, diagnostic and therapeutic procedures will be listed for the ARASEC ME-FAS, including: the participant identifier, age, race, ARASEC M-FAS flag, period of study procedure, procedure name, start date, and end date.

All radiotherapy will be listed (prior, concomitant, and follow-up) for the ARASEC ME-FAS, including: the participant identifier, age, race, ARASEC M-FAS flag, period of radiotherapy, intent, setting, type, whether radiotherapy was given to relieve skeletal symptoms, location, date of first fraction, date of last fraction, total cumulative dose (Gy).

6.10 Appendix 10: Treatment Compliance

Treatment compliance will be listed for the ARASEC ME-FAS, including: the participant identifier, age, race, ARASEC M-FAS flag, batch number, kit number, dispense status, date dispensed, amount of tablets dispensed (mg), date of return, amount of tablets returned (mg), amount of tablets used (mg), comments for any known discrepancies.

6.11 Appendix 11: AE Imputation Rules

Missing or incomplete AE start and end dates will be imputed according to the following rules.

Missing/Incomplete AE Start Date

- If day is missing but month and year are available, then the imputed day will be the first day of the month or the date of first dose if they have the same month and year.
- If day and month are missing but year is available, then the imputed day and month will be 01 Jan or the date of first dose if they have the same year.
- If day, month and year are all missing, impute start date as the date of first dose if participant was treated, or the date of enrollment if the participant was not treated.

If any of the imputed dates above are later than the non-imputed AE end date, then the AE start date should be set to the AE end date.

Missing/Incomplete AE End Date

- If day is missing but month and year are available, then the imputed day will be the last day of the month or end of study date if they have the same month and year.
- If day and month are missing but year is available, then the imputed day and month will be 31 Dec, or the end of study date if they have the same year.
- If day, month, and year are all missing, impute end date as the end of study date.

6.12 Appendix 12: Protocol Required Laboratory Assessments for Hematology and Chemistry

Laboratory Group	Laboratory Parameter
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit Mean corpuscular volume Mean corpuscular hemoglobin %Reticulocytes White blood cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry	Blood urea nitrogen Creatinine Glucose (fasting) Potassium Sodium Calcium Aspartate aminotransferase/Serum glutamic-oxaloacetic transaminase Alanine aminotransferase/Serum glutamic-pyruvic transaminase Alkaline phosphatase Total and direct bilirubin Total protein Albumin

6.13 Appendix 13: List of Abbreviations

Abbreviation	Definition
ADT	Androgen Deprivation Therapy
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CI	Confidence Interval
CRPC	Castration-Resistant Prostate Cancer
ME-FAS	Match Eligible Full Analysis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form

EOT	End of Treatment
M-FAS	Matched Full Analysis Set
GGT	Gamma-glutamyl Transferase
HLT	High Level Term
IPTW	Inverse Probability of Treatment Weighting
ITT	Intention-to-treat
KM	Kaplan Meier
LHRH	Luteinizing Hormone Releasing Hormone
LKAD	Last Known Alive Date
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
mHSPC	Metastatic Hormonesensitive Prostate Cancer
NCI CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
OS	Overall Survival
PCWG3	Prostate Cancer Clinical Trials Working Group
PD	Protocol Deviation
PFS	Progression-Free Survival
PH	Proportional Hazards
PSA	Prostate Specific Antigen
PT	Preferred Term
RECIST	Response Evaluation Criteria In Solid Tumors
rPFS	Radiographic Progression-Free Survival
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SC	Steering Committee
SD	Standard Deviation
SMD	Standardized Mean Difference
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
WHO-DD	World Health Organization - Drug Dictionary

6.14 Appendix 14: Changes to Protocol-Planned Analyses

All analyses where a comparable set of data from the CHAARTED study is not to be provided (i.e., all data except that relating to baseline variables for matching and the primary and secondary efficacy analyses) will be performed on the ARASEC ME-FAS, consisting of ARASEC participants only. This is a change from the protocol in that protocol section 9.4.5 specifies that selected safety analyses will be performed on the MSP, and this will not be possible in practice due to lack of comparable data from the CHAARTED study.

Abnormal findings observed during physical examinations will not be summarized per the protocol because the relevant data will not be collected in the eCRF.

7. References

Collett D. Modelling Survival Data in Medical Research. Chapman & Hall/CRC, New York, New York. . 2003.

Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N Engl J Med. 2015 Aug 20;373(8):737-46.

Yang D. and JE. Dalton, A Unified Approach to Measuring the Effect Size Between Two Groups using SAS®, Paper 335-2021, SAS Global Forum 2012.

Zhang Z. et al. Balance Diagnostics After Propensity Score Matching. Annals of translational medicine vol. 7,1 (2019): 16. doi:10.21037/atm.2018.12.10.