Document Type:	Statistical Analysis Plan
Official Title:	A 2-stage, Lead-In and Randomized, Phase 2, Open-label study of Darolutamide versus Enzalutamide as Monotherapy on Testosterone Levels Change in Men with Hormone-Naïve Prostate Cancer (ARAMON)
NCT Number:	NCT05526248
Document Date:	06 MAR 2024

Title Page

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Protocol Number: BAY 1841788 / 21953

Compound Number: BAY 1841788 / Darolutamide

Short Title: ARAMON: Evaluation of darolutamide versus enzalutamide monotherapy in men with hormone naïve Prostate Cancer

Acronym: ARAMON

Sponsor Name: Bayer HealthCare Pharmaceuticals, Inc.,
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Regulatory Agency Identifier Number(s):

Registry	ID
IND	114769
NCT	05526248

Date: 06 MAR 2024

Version: 3.0

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 ARAMON is based on the protocol Version 2.0 dated 10 AUG 2023.

SAP Version	Date	Change	Rationale
1.0	31 AUG 2022	Not applicable	Original version
2.0	18 JAN 2024	Section 1.1: Revise endpoint language in table 1-1 and 1-2.	Align with protocol v2.0
		Section 1.1: Add fasting insulin as an endpoint and footnotes updated in table 1-2.	Align with protocol v2.0
		Section 1.1: Remove Week 12 from testosterone secondary endpoint in tables 1-1 and 1-2.	Align with protocol v2.0 and remove redundancy with primary endpoint
		Section 1.2: Add details on data cut type used for the analysis	Clarification on what data to be used for the analysis
		Section 1.2.1: Add footnote to Figure 1-1	Align with protocol v2.0
		Section 1.2.1.2: Add EOT treatment visit details.	Align with protocol v2.0
		Section 1.2.1.3: Revise Active follow-up period definition.	Align with protocol v2.0
		Section 3: Change ‘met all inclusion exclusion criteria’ to ‘met all inclusion and none of the exclusion criteria’	Align with protocol v2.0
		Section 4.1.3: Remove ‘within +/- 7 days of scheduled date’	Account for baseline measures done outside the window
		Section 4.1.3: Clarify the nearest measure prior to the study drug administration date will be used for baseline	To include the baseline measures recorded in the ‘Unscheduled’ visit CRF pages
		Section 4.1.3: Revise the logic to choose the measurement for the analysis	Remove ambiguity around ‘scheduled date’ and to include ‘unscheduled’ post baseline measurement incase scheduled visits do not exist
		Section 4.2.1: Remove ‘darolutamide’ from the primary analysis timepoint for randomized phase	Align with protocol v2.0 that last participant could be on either arm in randomized phase
		Section 4.3.1.1 Change ‘absolute’ PSA response to ‘Undetectable’ PSA response, and 50% and 90% ‘relative’ PSA response to PSA50, PSA90.	Align with terminologies commonly used in other literature
		Section 4.3.1.1 Remove relative 30% PSA response (PSA30)	To focus on PSA50 and PSA90 since response rate in mHSPC is very high
		Section 4.3.1.1 Add 0.2 ng/mL detection limit value to PSA response rates definitions	Clarify detection limit
		Section 4.3.1.1 Add Breast enlargement, Breast mass, Breast swelling in gynecomastia	Summarize all AEs classified as feminizing side-effects
		Section 4.3.1.1 Add analysis of AEs of special interest associated with ARI treatment	Summarize common AEs associated with ARI treatment
		Section 4.3.1.2: Add ‘and a Toeplitz covariance structure’ to the SAS PROC MIXED details	Align with protocol v2.0

		Section 4.5: Remove language related to grading of laboratory measures	Laboratory measures are not graded in this study
		Section 4.5.2 Remove TEAEs with incidence of at least 5% table	Not meaningful with the sample size of the study
		Section 4.5.2 Add drug related TEAEs; add a comprehensive list of safety tables planned	Elaborate safety findings
		Section 4.6.1: Add free testosterone as exploratory analysis for lead-in phase primary analysis	Explore the treatment effect of darolutamide on free testosterone
		Section 4.6.1: Remove FACT-P and exploratory endpoints from lead-in primary analysis	Prioritizing the important endpoints for decision making to go into the randomized phase
		Section 6.1.1: Add Discontinued from treatment along with the primary reason for discontinuation in place of participants continued after treatment discontinuation	Align with clarification on active follow-up in protocol v2.0
		Section 6.1.2: Revise age groups	Align with ICH E7 Q&A (2010) recommendations
		Section 6.1.2: Add time from first progression and most recent relapse to first dose	Assess the disease progression
		Section 6.1.2: Add eGFR	Assess renal function
		Section 6.1.2: Revise list of baseline lab variables	Align with the endpoints planned to assess and to prioritize the important endpoints for lead-in primary analysis
		Appendix 5: Add PROC for primary endpoint analysis and corrections to the current code	Clarification and corrections
		Appendix 6: Corrections to the current code	Corrections
3.0	06 MAR 2024	Section 4.5.2: Add Treatment-emergent study drug-related adverse events of feminizing side effects by MedDRA SOC and PT and worst CTCAE grade	Assess the worst grades of each feminizing side-effect
		Section 4.6.1: Add PSA analysis with non-confirmed responses for Lead-in primary analysis	Since the study is ongoing
		Section 4.6.1: Add median treatment duration for Lead-in primary analysis	Study how long subjects were on treatment at the time of analysis
		Section 4.6.2: Add Feminizing side effects analysis by <=50% and >50% week 12 testosterone increase subgroups	Assess the adverse events profiles for subgroups
		Section 6.1.2: Remove baseline value presentation for Sex hormones and Fat and glucose metabolism for lead-in primary analysis	The important baseline summaries needed for decision making are in their respective endpoint tables
		Change AEs of special interest to AEs of special topics	For consistency across darolutamide studies

1. Introduction

The SAP describes the planned analyses of the ARAMON study, a Phase 2, Randomized, Open-label study of Darolutamide or Enzalutamide Monotherapy on Testosterone Levels in Men with Hormone-Naïve Prostate Cancer. Details included in the SAP include a description of endpoints, a brief description of the study design, analysis sets and statistical methodology.

ARAMON is designed to evaluate the efficacy and safety of treatment of men with hormone sensitive prostate cancer experiencing biochemical recurrence (BCR) with darolutamide or enzalutamide monotherapy. Efficacy outcomes measured will include serum testosterone levels, PSA levels and hormonal changes derived from the androgen axis including endocrine and energy metabolism markers and changes in bone mineral density. Study will also evaluate safety and quality of life, as well as fitness and physical function.

The analysis of the study will be conducted at three data cuts expected after about 12 weeks after start of darolutamide therapy for the lead-in phase, after 12 weeks post-randomization in the randomized phase and at end of the randomized phase. Table, figure and listing specifications are contained in a separate document.

Currently, there are no changes to the analyses described in the protocol amendment 1.0.

1.1. Objectives, Endpoints, and Estimands

Table 1-1: Lead-in phase objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the impact of darolutamide on serum testosterone level over a 12-week intervention period	Change in serum testosterone level from baseline to week 12
Secondary	
To evaluate the impact of darolutamide monotherapy on serum testosterone level over the course of a 52-week intervention period	Change in serum testosterone level from baseline at week 24 and 52
Assess PSA response rate	Serum PSA Week 4, 12, 24, 36, 52
To assess safety of darolutamide monotherapy in participants with hormone-naïve prostate Cancer with BCR	AE assessments using NCI CTCAE (v.5.0)

Abbreviations: BCR-Biochemical Recurrence, NCI CTCAE-National Cancer Institute Common Terminology Criteria for Adverse Events, PSA Prostate Specific Antigen.

Table 1-2: Randomized Phase Objectives and Endpoints

Objectives	Endpoints
Primary	
To compare the effects of treatment with darolutamide vs. enzalutamide monotherapy on serum testosterone level over a 12-week intervention period	Change in serum testosterone level from baseline to week 12
Secondary	
To compare the effect of darolutamide vs. enzalutamide monotherapy on serum testosterone level over the course of a 52-week intervention period	Change in serum testosterone level from baseline at week 24 and 52
Measure changes in markers of endocrine function related to sex hormones	Changes in the blood levels of sex hormones (DHT, DHEA, SHBG, LH, FSH, Androstenedione, Prolactin, Estradiol)
Measure changes in markers of components of fat and glucose metabolism	Changes blood levels of Total cholesterol, High-density and low-density lipoproteins, Triglycerides, Haemoglobin A1C, Fasting insulin, Fasting glucose, Fat body mass, Lean body mass
Assess PSA response rate	Serum PSA Week 4, 12, 24, 36, 52
To assess safety and QOL of darolutamide vs. enzalutamide monotherapy in participants with hormone-naïve prostate Cancer with BCR	AE assessments using NCI CTCAE (v.5.0) and FACT-P
Exploratory	
Evaluate changes in Bone turnover	Markers of bone turnover: BSAP, CTX, DEXA scan
Physical function*	Subjective physical function: Godin – 4 questions, PROMIS Fatigue – 8 questions, PROMIS Physical – 6 questions, Self-Efficacy – 9 questions

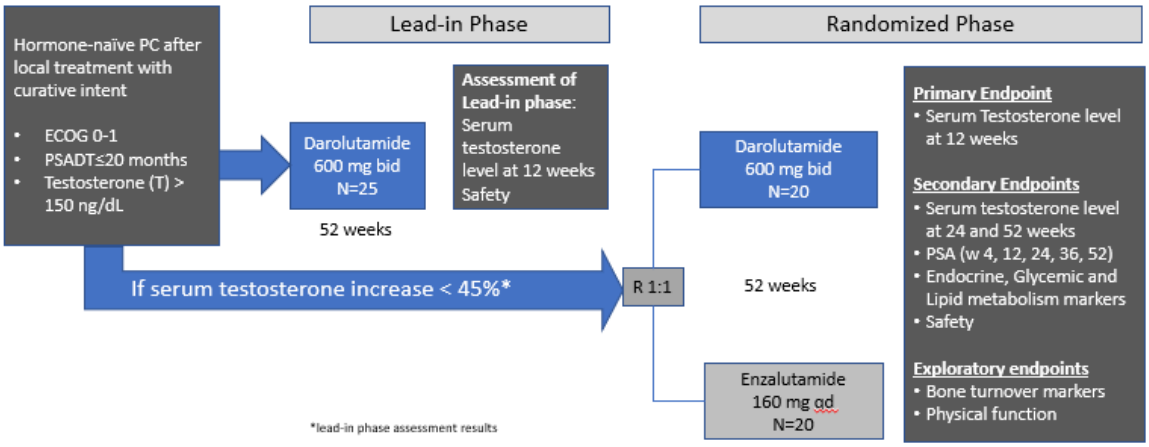
Abbreviations: A1C-glycated (hemoglobin), AE adverse events, BCR-Biochemical Recurrence, BSAP bone specific alkaline phosphatase, CTX C-telopeptid, DHEA-dehydroepiandrosterone, DHT-dihydrotestosterone, DEXA dual energy x-ray absorptiometry, FACT-P Functional Assessment of Cancer Therapy – Prostate Cancer, FSH-follicle-stimulating hormone, LH-luteinizing hormone, NCI CTCAE-National Cancer Institute-Common Terminology Criteria for Adverse Events, PSA-Prostate-specific antigen, QOL Quality of life, SHBG- sex hormone-binding globulin, PROMIS Patient-Reported Outcomes Measurement Information System.*The physical function assessments might be modified.

1.2. Study Design

1.2.1 Overall Design

This is a two-stage open-label phase 2 study with a lead-in single-arm phase and the randomized phase, to assess the impact of androgen receptor inhibitor (ARI) darolutamide or enzalutamide as a monotherapy treatment on serum testosterone levels in men with hormone-naïve prostate cancer experiencing BCR. The study design is shown in Figure 1-1.

Figure 1-1: Overall Design



Abbreviations: ECOG Eastern cooperative oncology group, PC prostate cancer, PSADT PSA doubling time.

In the lead-in phase, participants will be treated with darolutamide (600 mg twice daily). The primary analysis of the lead-in phase will occur when the last participant in the lead-in phase has been on treatment for 12 weeks, unless the participant discontinued due to lost to follow-up, withdrawal, or death. Analysis will be based on a date-based data cut in which the cutoff date will be the last participant week 12 visit date.

The study team will review the findings from the lead-in phase and provide input on interpretation of the results from the lead-in phase. This will help guide a decision on go/no-go with the randomized phase as well as potential changes in the study design for the randomized phase by the sponsor.

In case of the decision to proceed in the randomized phase, participants will be randomized in a 1:1 ratio to receive either darolutamide (600 mg twice daily) or enzalutamide (160 mg once daily). The primary analysis of randomized phase will be conducted when the last participant in the randomized phase has been on treatment for at least 12 weeks. Similar to lead-in phase the analysis will be based on a date-based data cut.

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

The overall sample size across the two phases is expected to be about 65 participants.

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

1.2.1.1 Screening period

After the participant has signed the Informed Consent Form (ICF), the screening period will begin from the date of signed ICF to up to 28 days before start of study intervention (date of first dose). Enrolled participants include those who signed the informed consent form, met all inclusion and none of the exclusion criteria, and are eligible for the first dose of study drug. The IWRS system will assign a unique participant ID to an enrolled participant.

1.2.1.2 Treatment period

The treatment period is defined as the time from the administration of first dose of study treatment until 52 weeks or 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.

End of treatment (EOT) visit takes place 30 days (+7 days) after the last dose.

1.2.1.3 Active Follow–up period

When the participant's treatment is discontinued before completing week 52 treatment, the participant will continue assessments until week 52. This follow-up period is defined as the Active Follow-up period.

1.2.2 Participant completion of study

A participant is considered to have completed the study if he has completed all periods of the study (see protocol Table 1.3 for lead-in phase, Table 1.4 for randomized phase, and Table 1.5 for active follow-up period), unless the participant discontinued due to lost to follow-up, withdrawal, or death.

1.2.3 End of Study Definition

The end of the study is defined as the date of the LPLV in the study.

LPLV of the study is reached when all participants have completed the last scheduled procedure shown in the Schedule of Activities including the active follow-up period.

2. Statistical Hypotheses

The core questions to be addressed in the two phases of the study are described in the following sections.

Lead-in Phase

Descriptive analyses will be provided for the lead-in phase without formal hypothesis testing.

Randomized Phase

The randomized phase will test the Null Hypothesis of no difference between the Darolutamide arm and the Enzalutamide arm on the primary endpoint of mean percent change in Testosterone from baseline to week 12, against the alternative hypothesis of a difference between arms at a two-sided 0.05 level. For mean percent changes of Δ_D and Δ_E in the Darolutamide and Enzalutamide arms these hypotheses can be expressed as

$$H_0: \Delta_D = \Delta_E \text{ vs. } H_1: \Delta_D \neq \Delta_E$$

2.1. Multiplicity Adjustment

Not applicable as there are no co-primary endpoints or interim analyses requiring special means for the control of the overall false positive error rate.

3. Analysis Sets

For purposes of analysis, the following populations are defined:

Table 3-1: Populations for analyses: Lead-in phase

Population	Description
Screened	All participants who sign the informed consent form
Evaluable	All enrolled participants having testosterone data at baseline and Week 12. Enrolled participants include those who signed informed consent and met all inclusion and none of the exclusion criteria.
Safety	All enrolled participants who received any darolutamide post-enrollment regardless of their eligibility for the study.

Table 3-2: Populations for analyses: Randomized Phase

Population	Description
Screened	All participants who sign the informed consent form
Evaluable	All randomized participants having testosterone data at baseline and week 12 who signed informed consent and met all inclusion and none of the exclusion criteria.
Safety	All randomized participants who received any quantity of study intervention, regardless of their eligibility for the study. The safety evaluation will be performed based on the intervention actually received.

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).

4. Statistical Analyses

4.1. General Considerations

All baseline variables will be reported using the appropriate statistics: categorical variables by frequency tables (frequencies and percentages) and continuous variables by sample statistics (i.e., mean, standard deviation, minimum, median, quartiles, and maximum). The number of participants screened will be summarized for both the lead-in and randomized cohorts.

The efficacy related endpoints will be evaluated in the evaluable population while the safety endpoints will be evaluated in the safety population.

Efficacy endpoints will consider data until last dose of study drug (while on treatment).

4.1.1 Analysis junctures

The analyses for this study will occur at three junctures as described in section 1.2.1. The endpoints analyzed at each juncture will be as follows:

- For primary analysis of the lead-in phase: Primary endpoint of percent change in testosterone; PSA responses at 4 and 12 weeks; incidence of treatment emergent adverse events with emphasis on feminizing side effects.
- For primary analysis of the randomized phase: Primary endpoint of percent change in testosterone; PSA responses at 4 and 12 weeks; other sex hormone changes at 4 and 12 weeks; components of fat and glucose metabolism at 4 and 12 weeks; incidence of treatment emergent adverse events with emphasis on feminizing side effects.
- Final analysis: Separate analyses will be performed for the lead-in phase and the randomized phase of the study. For the lead-in phase, summaries for visits after 12 weeks will be presented for testosterone, PSA, and safety endpoints. For the randomized phase, summaries at the visits after week 12 will be presented for testosterone, sex hormones, components of fat and glucose metabolism, and additional efficacy and safety endpoints.

4.1.2 Handling missing data

All missing or partial data will be presented in the participant data listing as they are recorded on the Case Report Form. Except as noted, missing data will not be estimated or carried forward in any statistical analysis.

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

Incomplete death dates:

Every effort should be made to resolve incomplete or missing dates during the course of the study (i.e., edit checks, data cleaning/monitoring etc.). However, in rare circumstances, missing parts of either the censoring date or the event date may occur where an imputation algorithm must be defined. In general, the following rule should be followed: A missing month or year is not acceptable. To impute a value for day, day 15 of the month will be used for the calculation.

Partial or missing AE dates:

Refer to Appendix 1: Imputation rule for partial missing dates for the imputation rule for incomplete AE dates.

Laboratory Assessments:

To facilitate the transformation of the data, the least detectable values of Testosterone and other laboratory values will be used when the baseline data notes a less than detectable value. When such a value is not uniformly available across sites, then the lowest value of the laboratory analyte across participants at baseline in the data cut will be used.

FACT-P Questionnaire:

For FACT-P, total scores and subscale scores (physical well-being, social/family well-being emotional well-being, and functional well-being) will be assessed. Where there are missing items, subscale scores will be prorated if >50% of items on subscale are completed. This will be done by multiplying the sum of the subscale by the number of items in the subscale, then dividing it by the number of items answered. If ≤50% of the items are answered for any domain, then the score of that domain will be set to missing (see scoring of FACT-P in Appendix 2: Scoring procedures for FACT-P). The total score will be set to missing if the related overall item response rate is less than or equal to 80% (without prorated subscale items). In addition, a total score will only be calculated if all the component subscales have valid scores.

The statistical evaluation will be performed by using the software SAS (release 9.4 or higher; SAS Institute Inc., Cary, NC, USA. All data will be presented in the participant data listing as they are recorded on the Case Report Form (CRF), i.e., partially missing data will appear as such.

4.1.3 Data rules

In case of repeated measurements over multiple dates per time point,

- For baseline, the nearest visit (scheduled or unscheduled) to the start of the study drug administration will be used;
- For post-baseline measures, the scheduled visit will be used. Unscheduled visits will be used if there are no scheduled visits – then the first unscheduled visit will be used.

If there are repeated measurements per time point on the same day (e.g., laboratory values, vital signs, etc.),

- For baseline, the latest measurement will be used;
- at any post baseline time point, the first measurement at the visit will be used.

4.2. Primary Endpoint Analysis

The primary endpoint, percent change in testosterone, is defined in Section 1.1. The primary endpoint for both phases will be analyzed using a natural logarithm transformation consistent with sample size assessments in Section 5 given a distribution for the endpoint which is skewed right. Further, the percent change endpoint is a re-scaled fold change from baseline statistic for which such a transformation is often conducted. The mean fold change and

percent change estimates are interpretable as geometric means given the logarithmic transformation.

The primary endpoint will be analyzed in the evaluable population.

4.2.1 Main Analytical Approach

The primary endpoint for the lead-in phase will be analyzed at 12 weeks after start of darolutamide for the last participant in the lead-in phase. If the study continues into the randomized phase, the primary endpoint analysis for the randomized phase will be conducted 12 weeks after start of study treatment for the last participant in the randomized phase.

4.2.1.1 Lead-in Phase

The participant testosterone levels at baseline and week 12 will be transformed to natural logarithm values. The mean and 95% Confidence Interval of the differences between the week 12 and baseline values will be computed and back transformed by exponentiation to obtain the mean fold change M_F with its 95% Confidence Interval [L_F, U_F]. The mean percent change Δ can be obtained as $\Delta = 100*(M_F-1)$ with Confidence Interval [$100*(L_F-1)$, $100*(U_F-1)$]. In addition to the estimated mean percent change and its confidence interval, summary statistics will include the mean fold change with confidence intervals, and the mean, standard deviation, median, quartiles, minimum, and maximum of percent change computed from the raw week 12 and baseline testosterone values.

4.2.1.2 Randomized Phase

The participant level differences between the natural log transformed testosterone values at week 12 and baseline will be computed. These differences will be compared across the darolutamide and enzalutamide arms using a two-sample t-test. SAS code will be similar to code shown in Appendix 4: Randomized phase primary endpoint analysis for natural logarithm transformed Testosterone. Two-sided p-values from this t-test will be reported to assess whether the null hypothesis can be rejected in favor of the alternate hypothesis described in Section 2. Additionally, the estimated difference between darolutamide and enzalutamide and the 95% confidence limits from the t-test will be back transformed by exponentiation to obtain the ratio of the fold change in testosterone values from baseline for darolutamide to that for enzalutamide and the confidence limits for this estimate. Within treatment group, mean percent change and confidence intervals as well as other summary statistics described for the lead-in phase will also be reported.

4.3. Secondary Endpoint Analysis

All secondary endpoints, as described in Section 1.1, will be analyzed in the evaluable population except for the safety endpoints, which will be analyzed in the safety population.

4.3.1 Main Analytical Approach

The secondary endpoints summarized at each juncture of the study are detailed in Section 4.1. The analysis approach for each secondary endpoint at each phase is as follows.

4.3.1.1 Lead-in Phase

- Testosterone at weeks 24 and 52:

The differences between the log transformed data at the visit and baseline will be estimated with 95% Confidence Intervals using SAS PROC MIXED with the ESTIMATE statement. These will be transformed to mean percent change and 95% confidence intervals using the same steps as for the primary analysis in the lead-in phase. SAS code will be similar to code shown in Appendix 5: Lead-in phase analysis for natural logarithm transformed Testosterone and other endpoints using the log transformation. Results for testosterone at week 24 and 52 will be summarized in a similar manner to the primary endpoint and depicted graphically over time with 95% confidence intervals at each visit.

- PSA responses:
    - Undetectable PSA response

Undetectable PSA is defined as a baseline PSA value above the 0.2 ng/mL detection limit and a post baseline PSA level below 0.2 ng/mL, confirmed by a second subsequent PSA value below 0.2 ng/mL 3 or more weeks later, with all potential PSA values between the initial date and the confirmation date below 0.2 ng/mL.

The undetectable PSA response is defined as the number of participants with undetectable PSA divided by the total number of participants evaluable. The undetectable PSA response will be summarized at 4, 12, 24, 36 and 52 weeks.

- PSA50, PSA90

PSA50 is defined as a baseline PSA value above the 0.2 ng/mL detection limit and a post baseline ≥50% reduction of the PSA level compared to the baseline value, confirmed by a second subsequent PSA value with a ≥50% reduction from baseline 3 or more weeks later, with all potential PSA values between the initial date and the confirmation date showing a ≥50% reduction from baseline. PSA90 is defined in the same way with 90% reduction.

The PSA50 response is defined as the number of participants with PSA50 divided by the total number of participants evaluable. The PSA90 response is defined the same way. PSA50 and PSA90 will be summarized at 4, 12, 24, 36 and 52 weeks.

In addition, descriptive statistics will be provided for PSA maximum percent decline of ≥ 50%, ≥ 90% from baseline at any time on study.

- Analysis of AEs:

All grades of the feminizing side effects of gynecomastia (including breast enlargement, breast mass, breast swelling), breast tenderness/pain, nipple pain, and hot flush will be summarized using frequencies and percentages. Incidence of AEs of special topics (Bone fractures excluding pathological fractures, Cerebral ischemia, Diabetes mellitus and Hyperglycaemia, Fall, Fatigue/ asthenic conditions, Weight decreased, Rash, Seizure, Hypertension, Vasodilatation and flushing, Mental impairment disorders, Depressed mood disorders, Breast disorders/gynecomastia, Cardiac disorders, Cerebral and intracranial hemorrhage) associated with ARI treatment will also be presented.

4.3.1.2 Randomized Phase

- Testosterone at weeks 24 and 52:

The differences between the log transformed data at the visit and baseline will be compared across treatment groups with 95% Confidence Intervals using SAS PROC MIXED with the SLICE option and a Toeplitz covariance structure. These will be

transformed to the ratio of the fold change from baseline for darolutamide to that for enzalutamide and 95% confidence intervals using the same steps as for the primary analysis in the randomized phase. SAS code will be similar to code shown in Appendix 6: Randomized phase analysis for natural logarithm transformed Testosterone and other endpoints using the log transformation. Results will be summarized in a similar manner to the primary endpoint and will be summarized graphically using the mean percent change over time with 95% confidence intervals at each visit by treatment group, flagging visits where differences are significant at the nominal 0.05 and 0.01 levels.

- Sex hormones:

Will be analyzed at week 4, 12, 24 and 52 similar to testosterone.

- Components of fat and glucose metabolism:

Will be analyzed at week 4, 12, 24 and 52 similar to testosterone.

- PSA responses

Will be compared descriptively across treatments at weeks 4, 12, 24, 36 and 52 using frequencies and percentages.

- FACT-P

Differences in the FACT-P prostate cancer subscale and total will be summarized at each visit using PROC Mixed with the SLICE option, and the mean subscale and total scores will be depicted graphically over time with 95% confidence intervals at each visit by treatment group, flagging visits where differences are significant at the nominal 0.05 and 0.01 levels. The scoring procedure for FACT-P is elaborated in Appendix 2: Scoring procedures for FACT-P.

- Analysis of AEs:

All grades of the feminizing side effects of gynecomastia (including breast enlargement, breast mass, breast swelling), breast tenderness/pain, nipple pain, and hot flush, will be summarized using frequencies and percentages by treatment group.

4.4. Other Exploratory Endpoints

- Markers of bone turnover:

Will be analyzed for the randomized phase as described for the sex hormones and components of fat and glucose metabolism in Section 4.3.1.2.

- Physical function measures:

Will be summarized graphically as described for the FACT-P subscale in Section 4.3.1.2. The scoring procedures for PROMIS physical function questionnaires are elaborated in Appendix 3: Scoring for PROMIS.

4.5. Safety Analyses

All safety analyses will be descriptive and will be performed on the safety population. Safety data will be summarized descriptively for the lead-in phase and by treatment group for the randomized phase.

All AEs will be coded using the latest version prior to database lock of the Medical Dictionary for Regulatory Activities (MedDRA).

NOTE: AEs will be presented with their worst NCI-CTCAE grade.

4.5.1 Extent of Exposure

Study drug is defined as darolutamide for the lead-in, and darolutamide and enzalutamide for the randomized phase. As a 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 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.

4.5.2 Adverse Events

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

An overview of TEAEs will be summarized for the appropriate safety analysis set at the three data cuts. The following summaries will be done.

- Overview of TEAEs
- TEAEs by MedDRA ad worst CTCAE grade
- TEAEs by MedDRA ad worst CTCAE grade 3, 4 or 5
- TEAEs: number of subjects by primary SOC and PT
- TEAEs leading to permanent discontinuation of study drug: number of subjects by primary SOC and PT
- Number of subjects with TEAE by PT in decreasing order
- Drug-related TEAEs: number of subjects by primary SOC and PT

- Drug-related TEAEs leading to permanent discontinuation of study drug: number of subjects by primary SOC and PT
- Number of subjects with drug-related TEAE by PT in decreasing order
- SAEs: number of subjects by primary SOC and PT
- TESAEs: number of subjects by primary SOC and PT
- Drug-related TESAEs: number of subjects by primary SOC and PT
- TE non-SAEs (excluding TESAEs): number of subjects by primary SOC and PT

Additionally, feminizing side effects as described in Section 4.3, will be summarized by

- Overview of TEAEs of feminizing side effects
- Number of subjects with TEAEs of feminizing side effects by PT in decreasing order
- Treatment-emergent study drug-related adverse events of feminizing side effects by MedDRA SOC and PT and worst CTCAE grade
- Number of subjects with TEAEs of feminizing side effects leading to permanent discontinuation of study drug by PT in decreasing order
- Number of subjects with drug-related TEAEs of feminizing side effects by PT in decreasing order
- Number of subjects with drug-related TEAEs of feminizing side effects leading to permanent discontinuation of study drug by PT in decreasing order
- SAEs of feminizing side effects: number of subjects by primary SOC and PT
- TESAEs of feminizing side effects: number of subjects by primary SOC and PT
- Drug-related TESAEs of feminizing side effects: number of subjects by primary SOC and PT

AEs of special topics will be summarized by

- Number of subjects with special topics for adverse events

4.6. Other Analyses

4.6.1 Lead-in Phase Analyses

For the lead-in phase primary analysis: change in free testosterone from baseline to week 12, will be analyzed similar to serum testosterone. PSA response analysis summarized in section 4.3.1.1 will be repeated with non-confirmed PSA responses. Data collected on the CRF for Serum and Free testosterone, PSA, sex hormones, fat and glucose metabolism will be summarized in spider plots to support any changes to data collection for the randomized phase, or for additional support of the randomized phase findings. The median treatment duration will be presented in months. For subjects ended treatment before the data cut-off date, duration will be ‘last dose date – first dose day +1’. For subjects on treatment by the day of data cut-off, the duration will be ‘data cutoff date – first dose day +1’.

For the lead-in phase final analysis: for the sex hormones and the components of fat and glucose metabolism at weeks 4, 12, 24 and 52, the differences between the log transformed

data at the visit and baseline will be estimated with 95% Confidence Intervals using SAS PROC MIXED with the ESTIMATE statement. These will be transformed to mean percent change and 95% confidence intervals using the same steps as for the primary analysis in the lead-in phase. SAS code will be similar to that shown in Appendix 5: Lead-in phase analysis for natural logarithm transformed Testosterone and other endpoints using the log transformation. Sex hormones and fat and glucose metabolism endpoints will be depicted graphically over time with 95% confidence intervals at each visit.

The FACT-P prostate cancer subscale scores will be summarized at each visit using PROC Mixed with the ESTIMATE statement and depicted graphically over time with 95% confidence intervals at each visit.

The physical function scores will be summarized graphically using the methods described above for FACT-P.

4.6.2 Subgroup Analyses

For lead-in phase primary analysis:

- Overview of treatment-emergent adverse events of feminizing side effects, Number of subjects with treatment-emergent study drug-related adverse events of feminizing side effects by preferred term in decreasing order, Number of subjects with treatment-emergent study drug-related adverse events of feminizing side effects by worst CTCAE grade will be presented for the <=50% and >50% week 12 testosterone increase subgroups.

4.7. Interim Analyses

No group sequential interim analyses are planned. However, the analysis will be conducted at three junctures as described in Section 1.

4.8. Changes to Protocol-planned Analyses

There are no changes to the analyses described in the protocol.

5. Sample Size Determination

The sample sizes corresponding to the planned analysis methodology are provided below.

Lead-in Phase

Approximately 25 participants will be assigned to darolutamide to achieve at least 20 evaluable participants. This sample size will help estimate the mean percent change in serum testosterone level at 12 weeks with a 95% confidence interval having a half-width of no more than 25%, assuming a true mean percent increase of less than 45% and a standard deviation of 65%. This assessment uses a log normal distribution for percent change.

Randomized Phase

Contingent on the results of the evaluation in Section 1.2.1, the randomized phase statistical assumptions may be revised, or the study could be terminated after lead-in.

Should the study continue to the Randomized phase unmodified, a maximum of 40 participants (20 per arm) will be randomly assigned to study treatment (darolutamide or enzalutamide) such that approximately 34 evaluable participants complete the study. The randomized stage will require a sample size of 20 per group to provide 85% power to test the null hypothesis of no difference between groups on mean percent change at the two-sided 0.05 level. This assessment is based on a mean percent change in Testosterone from baseline and Standard Deviation for the Darolutamide arm of 45% and 65% versus 110% and 75% respectively for Enzalutamide and assumes a log normal distribution for percent change.

6. Supporting Documentation

6.1. Population Characteristics

6.1.1 Disposition of participants

Overall summaries will be presented for the lead-in phase, and by treatment arm as well for the randomized phase.

The number and the percentages of participants for the following will be summarized:

- Screened, Evaluable and Safety populations
- Discontinued from screening along with the primary reason for discontinuation
- Discontinued from treatment along with the primary reason for discontinuation
- Discontinued from active follow-up along with the primary reason for discontinuation

6.1.2 Demographics and baseline characteristics

Overall descriptive summaries of demographics and baseline characteristics will be presented for the lead-in phase, and by treatment arm as well for the randomized phase on the Evaluable population.

The following demographic data will be summarized:

- Age (years)
- Age category (<65, 65–74, 75–84, ≥85 years)
- Ethnicity
- Race
- Weight (kg)
- BMI (kg/m^2)

The following baseline characteristics will be summarized:

- ECOG Performance Status
- Stage of prostate cancer at initial diagnosis
- Gleason score of prostate cancer (<8, ≥8) at initial diagnosis
- Stage of prostate cancer at study entry
- Serum testosterone group (< 150 ng/dL, ≥ 150 ng/dL)
- Time from initial diagnosis to first dose of study drug (months)
- Bone lesions at baseline (Y/N)
- Number of bone lesions at baseline
- Hepatic function at baseline:
    - Normal: Total bilirubin and AST ≤ upper limit of normal (ULN)

  - Mild impairment: Total bilirubin > ULN to 1.5 x ULN or (Total bilirubin ≤ ULN and AST > ULN)
  - Moderate impairment: Total bilirubin > 1.5 to 3 x ULN, any AST
  - Severe impairment: Total bilirubin > 3 x ULN, any AST.
- Estimated glomerular filtration rate (eGFR) at baseline:
  - eGFR = [(140 - Age) x Weight/(72 x Creatinine)].

The following baseline lab values, assessed in secondary and exploratory endpoints, will be summarized in a separate baseline table:

- Serum testosterone
- Free testosterone
- PSA
- Sex hormones
- Fat and glucose metabolism
- FACT-P
- Bone turnover
- Physical function

6.1.3 Prior anti-cancer therapies

The prior systemic anti-cancer therapy summaries and summaries of prior radiotherapies and surgeries will be presented for the lead-in phase, and by treatment arm as well for the randomized phase on the Evaluable population.

6.1.4 Important protocol deviations

The number of participants with important protocol deviations will be presented by treatment arm and overall. The frequencies of each important protocol deviation will be presented by treatment arm and overall. All COVID-19 pandemic related protocol deviations are considered important protocol deviations and will be presented by treatment arm and overall.

Appendix 1: Imputation rule for partial missing dates

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

Appendix 2: Scoring procedures for FACT-P

FACT-P Scoring Guidelines (Version 4)

Instructions: 1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated and sum individual items to obtain a score.

3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. Add subscale scores to derive total scores (TOI, FACT-G & FACT-P).
5. **The higher the score, the better the QOL.**

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

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

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

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

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

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

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

Sum individual item scores: _____

Multiply by 7: _____
Divide by number of items answered: _____=**FWB subscale score**

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

Sum individual item scores:_____
Multiply by 12: _____
Divide by number of items answered: _____=**PC Subscale score**

To derive a FACT-P Trial Outcome Index (TOI):

Score range: 0-104

_____ (**PWB** score) + _____ (**FWB** score) + _____ (**PCS** score) =_____=**FACT-P TOI**

To Derive a FACT-G total score:

Score range: 0-108

_____ (**PWB** score) + _____ (**SWB** score) + _____ (**EWB** score) + _____ (**FWB** score) =_____=**FACT-G Total score**

To Derive a FACT-P total score:

Score range: 0-156

_____ (**PWB** score) + _____ (**SWB** score) + _____ (**EWB** score) + _____ (**FWB** score) + _____ (**PCS** score) =_____=**FACT-P Total score**

Appendix 3: Scoring for PROMIS

To find the total raw score for a short form with all questions answered, sum the values of the response to each question. For example, for the adult 8-item form, the lowest possible raw score is 8; the highest possible raw score is 40. In cases where individual items are skipped, the total raw scores can be prorated using the average of the raw scores of the complete items. This is acceptable as long as more than 50% of the items were answered at that specific visit. The prorated total raw scores with decimals should be rounded to the nearest whole number to translate to the corresponding T-score.

The tables below are used to translate the total raw score into a T-score for each participant. The T-score rescales the raw score into a standardized score with a mean of 50 and a standard deviation (SD) of 10. Therefore, a person with a T-score of 40 is one SD below the mean.

Fatigue 8a - Adult v1.0		
Short Form Conversion Table		
Raw Score	T-score	SE*
8	33.1	4.8
9	38.5	2.7
10	41.0	2.2
11	42.8	2.0
12	44.3	1.9
13	45.6	1.8
14	46.9	1.8
15	48.1	1.8
16	49.2	1.8
17	50.4	1.8
18	51.5	1.7
19	52.5	1.7
20	53.6	1.7
21	54.6	1.7
22	55.6	1.7
23	56.6	1.7
24	57.5	1.7
25	58.5	1.7
26	59.4	1.7
27	60.4	1.7
28	61.3	1.7
29	62.3	1.7
30	63.3	1.7
31	64.3	1.7
32	65.3	1.7
33	66.4	1.7
34	67.5	1.7
35	68.6	1.7
36	69.8	1.8
37	71.0	1.8
38	72.4	2.0
39	74.2	2.4
40	77.8	3.7

*SE = Standard Error on T-score !

PROMIS Fatigue 8a form

Adult v2.0 – Physical Function 6b		
Short Form Conversion Table		
Raw Summed Score	T-score	SE*
6	21.0	3.8
7	25.0	2.7
8	27.1	2.4
9	28.8	2.2
10	30.1	2.1
11	31.3	2.0
12	32.3	2.0
13	33.2	1.9
14	34.2	1.9
15	35.0	1.9
16	35.9	1.9
17	36.8	1.9
18	37.6	1.9
19	38.5	1.9
20	39.3	1.9
21	40.2	1.9
22	41.2	1.9
23	42.1	1.9
24	43.2	2.0
25	44.3	2.0
26	45.6	2.2
27	47.1	2.3
28	48.9	2.7
29	51.3	3.0
30	59.0	6.2
*SE = Standard Error on T-score metric		

PROMIS Physical Function 6b form

Appendix 4: Randomized phase primary endpoint analysis for natural logarithm transformed Testosterone

Following data structure will be obtained for the Input dataset LN_DATA. LN_Change will be the difference between the LN(Testosterone) values at Visit 12 from the LN value at baseline.

Subjid	trt	LN_Change
[redacted]	Daro	0.5
[redacted]	Daro	0.9
....		
[redacted]	ENZA	0.5
[redacted]	ENZA	0.8

The following SAS code will be used for the two-sample t-test.

```
PROC TTEST DATA=LN_DATA SIDES=2 ALPHA=0.05 H0=0;
        CLASS TRT;
        VAR LN_CHANGE;
RUN;
```

Appendix 5: Lead-in phase analysis for natural logarithm transformed Testosterone and other endpoints using the log transformation

For the primary end point analysis, PROC TTEST procedure similar to Appendix 4: Randomized phase primary endpoint analysis for natural logarithm transformed Testosterone will be used without the CLASS statement.

For the lead-in phase, the following data structure will be obtained for the input dataset LN_DATA to Proc Mixed. LN_Change will be the difference between the LN(Testosterone) values at Visit from the LN value at baseline. During the lead-in phase there will be no enzalutamide data.

Subjid	trt	visit	LN_Change
[redacted]	Daro	WK2	0.5
[redacted]	Daro	WK4	0.9
[redacted]	Daro	WK8	1.3
[redacted]	Daro	WK16	1.6
[redacted]	Daro	WK24	1.7
[redacted]	Daro	WK36	1.7
[redacted]	Daro	Wk52	1.6
[redacted]	Daro	WK2	0.4
[redacted]	Daro	WK4	1.3
....			

Following PROC Mixed code will be used.

```
PROC MIXED DATA = LN_DATA;
        CLASS VISIT SUBJID;
```

```
        MODEL LN_CHANGE = VISIT /DDFM = KR;
        RANDOM SUBJID;
        REPEATED / TYPE = TOEP SUBJECT=SUBJID;
        LSMEANS VISIT/ CL;
RUN;
```

Then the estimate for VISITS WK24 and WK52 will be retained. The dataset will have 2 lines. The fold change pair for each fold change (FC) can be computed as:

```
FC = EXP(Estimate);
LCL_FC = EXP(Estimate - StdErr*quantile('T', .975, DF));
UCL_FC = EXP(Estimate + StdErr*quantile('T', .975, DF));
```

These fold changes can be converted to Percent Change as:

```
PC = (FC-1)*100;
LCL_PC = (LCL_FC -1)*100;
UCL_PC = (UCL_FC -1)*100;
```

Similar code will be used for the other endpoints using the same transformation.

Appendix 6: Randomized phase analysis for natural logarithm transformed Testosterone and other endpoints using the log transformation

The following data structure will be obtained for the input dataset LN_DATA to Proc Mixed. LN_Change will be the difference between the LN(Testosterone) values at Visit from the LN value at baseline.

Subjid	trt	visit	LN_Change
[redacted]	Daro	WK2	0.5
[redacted]	Daro	WK4	0.9
[redacted]	Daro	WK8	1.3
[redacted]	Daro	WK16	1.6
[redacted]	Daro	WK24	1.7
[redacted]	Daro	WK36	1.7
[redacted]	Daro	Wk52	1.6
[redacted]	Daro	WK2	0.4
[redacted]	Daro	WK4	1.3
....			
[redacted]	ENZA	WK2	0.5
[redacted]	ENZA	WK4	2.2
[redacted]	ENZA	WK8	2.6
[redacted]	ENZA	WK16	2.8
.....			

The following PROC Mixed code will be used.

```
PROC MIXED DATA = LN_DATA;
        CLASS TRT VISIT SUBJID;
        MODEL LN_CHANGE = TRT|VISIT /DDFM = KR;
        RANDOM SUBJID(TRT);
        REPEATED / TYPE = TOEP SUBJID(TRT);
        LSMEANS TRT*VISIT/ DIFF SLICE = VISIT;
RUN;
```

Output the dataset created by LSMEANS. The data will be of the form:

Obs	Effect	Trt	Visit	_Trt	_Visit	Estimate	StdErr	DF	t-value	Probt
1	TRT*VISIT	Daro	WK2	Daro	WK4	0.4	0.3	XXX	xxx	0.xx
2	TRT*VISIT	Daro	WK2	Daro	WK8	0.8	0.32	XXX	xxx	0.xx
.....										
	TRT*VISIT	Daro	WK2	ENZA	WK2	-0.2	0.31	XXX	xxx	0.xx
.....										
	TRT*VISIT	Daro	WK52	ENZA	WK52	0.4	0.3	XXX	xxx	0.xx

From this dataset the records where 'Trt NE _Trt', where Trt = 'Daro', where 'Visit = _Visit' and Visit IN ('WK24','WK52") will be selected. This will select the two records where we are reporting results per the secondary objective. The fold change ratio (FCR) and the lower (LCL) and upper (UCL) confidence intervals for the fold change ratio will be obtained as:

```
FCR = EXP(Estimate);
LCL_FCR = EXP(Estimate - StdErr*quantile('T', .975, DF));
UCL_FCR = EXP(Estimate + StdErr*quantile('T', .975, DF)));
```

For fold change (FC) within treatment, the PROC MIXED will be repeated above with the following LSMEANS statement:

```
LSMEANS TRT*VISIT/ CL;
```

Then the estimate for the Daro and ENZA for VISITS WK24 and WK52 will be retained. The dataset will have 6 lines. The fold change pair for each FCR can be computed as

```
FC = EXP(Estimate);
LCL_FC = EXP(Estimate - StdErr*quantile('T', .975, DF));
UCL_FC = EXP(Estimate + StdErr*quantile('T', .975, DF));
```

These fold changes can be converted to Percent Change as:

```
PC = (FC-1)*100;
LCL_PC = (LCL_FC -1)*100;
UCL_PC = (UCL_FC -1)*100;
```

Similar code can be used for the other endpoints using the same transformation.

Appendix 7: List of Abbreviations

ADT	Androgen deprivation therapy
AE	Adverse event
AR	Androgen receptor
ARI	Androgen receptor inhibitor
BCR	Biochemical relapse
BMD	Bone mineral density
BSAP	Bone specific alkaline phosphatase
CI	Confidence interval
eCRF	Electronic case report form
CPET	Cardiopulmonary exercise test
CTCAE	Common Terminology Criteria for Adverse Events
CTX	C- Telopeptid
DEXA	Dual energy x-ray absorptiometry
DHT	Dihydrotestosterone
DHEA	Dehydroepiandrosterone
EC	Ethics committee
ECOG - PS	Eastern Cooperative Oncology Group Performance Status
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
FACT-P	Functional Assessment of Cancer Therapy – Prostate Cancer
FAS	Full analysis set
FSH	Follicle-stimulating hormone
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRB	Institutional review board
ITT	Intent-to-treat
IWRS	Interactive web randomization system
LH	luteinizing hormone
LPLT	Last participant last treatment
LPLV	Last participant last visit
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCI - CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
PROMIS	Participant reported outcome measurement information system
PSA	Prostate-specific antigen
PSADT	PSA doubling time
PT	Preferred term
QOL	Quality of life
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
TSH	Thyroid stimulating hormone
SHBG	Sex hormone binding globulin

TEAE	Treatment emergent adverse events
TESAE	Treatment emergent serious adverse events