Janssen Research & Development

Statistical Analysis Plan

A Multi-center, Open-label, Single-arm Phase 2 Study of the Adjuvant Treatment of Apalutamide and Androgen Deprivation Therapy (ADT) in Treatment-naïve Participants Who Have Undergone Radical Prostatectomy (RP) for Non-metastatic Prostate Cancer and Who Are at High Risk for Metastases

Protocol 56021927PCR2041; Phase 2

JNJ-56021927 (Apalutamide)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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VERSION HISTORY

Table 1 – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1.0	18-Aug-2020	Not Applicable	Pre-FPI Stable version
2.0	14-Dec-2023	Update general considerations 5.1	Provided a conservative approach for confidence intervals of survival function at specific time point in case no events have occurred by the given time point

1. INTRODUCTION

This statistical analysis plan (SAP) describes the definitions of analysis sets, derived variables, and statistical methods for all planned statistical analyses for protocol 56021927PCR2041.

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess if the combination of apalutamide and ADT in participants with high-risk localized prostate cancer improves the BCR-free rate.	• BCR-free rate at 24 months. BCR is defined as a confirmed PSA >0.2 ng/mL.
Secondary	
• To determine the BCR-free rate at 12 months.	• BCR-free rate at 12 months.
• To determine the time to serum testosterone recovery.	• Testosterone recovery rate at 18 and 24 months.
Exploratory	
• To evaluate the incidence of rash.	• Incidence of rash.

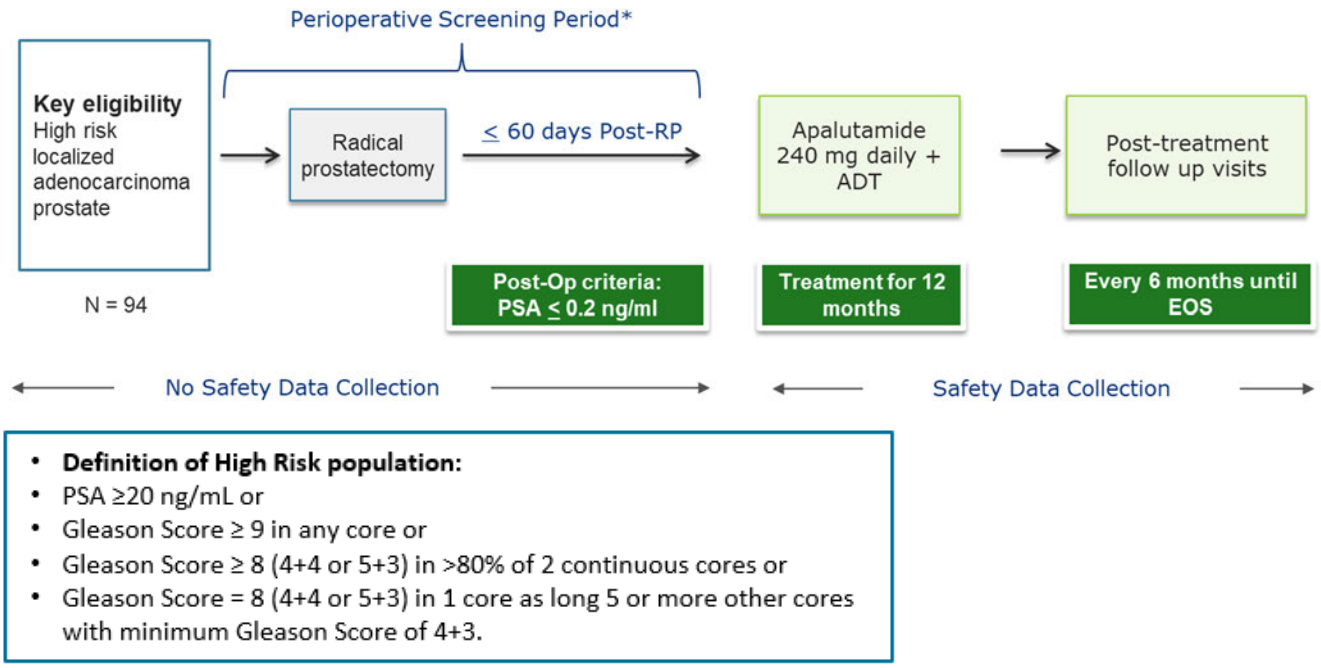
Key: ADT=androgen-deprivation therapy; BCR=biochemical recurrence; PSA=prostate-specific antigen

1.2. Study Design

This is a single-arm, open-label, multi-center study of apalutamide and ADT in 96 participants with high risk localized prostate cancer who are treatment naïve, documented to have no evidence of metastatic disease prior to study entry, who are no more than 60 days post radical prostatectomy (RP), whose prostate-specific antigen (PSA) is ≤0.2 ng/mL at study entry and who have recovered from surgery, per the clinical judgement of the investigator.

There will be one intervention group receiving apalutamide with ADT of investigator's choice (3-month depot preferred) for 12 months. Treatment with apalutamide and ADT will start following screening and completion of RP and no later than postoperative Day 60. Approximately 30 days post-treatment, a safety follow-up examination will be completed (end of treatment visit). There will be a follow-up period during which serum PSA and testosterone levels will be measured and clinical status monitored every 6 months after the completion of treatment until the end of the study (EOS). The EOS is defined as the date of last participant's enrolment + 24 months or discontinuation of all study participants from the study, whichever occurs first. Study enrollment is defined as the day when the participant receives the first dose of apalutamide after having met all pre-screening criteria.

A diagram of the study design is provided below.



Key: ADT=androgen deprivation therapy; EOS=end of study; N=number of participants; post-op=postoperative; PSA=prostate-specific antigen; RP=radical prostatectomy.

2. STATISTICAL HYPOTHESES

The primary hypothesis of this study is that adjuvant treatment with apalutamide and ADT will improve the BCR-free rate at 24 months in the treatment-naïve, non-metastatic prostate cancer population who are at high risk for the development of metastases. The null hypothesis is that the BCR-free rate at 24 months is ≤ 76%.

3. SAMPLE SIZE DETERMINATION

It is assumed that BCR-free rate follows an exponential distribution with a constant hazard rate. It is estimated that approximately 94 participants accrued over approximately 1 year, treated for 12 months and followed for an additional 12 months would be required to provide at least 80% power in detecting a 10% absolute increase in BCR-free rate at 24 months of 76%[1] to 86% at a 1-tailed significance level of 0.05. Sample size was calculated using PASS 15 (Power Analysis and Sample Size Software [2017][2] .

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Following analysis sets will be defined for analysis purposes.

- Safety Analysis Set: The safety analysis set will consist of all participants who received at least 1 dose of apalutamide. All safety analyses will be performed using the safety analysis set.

- Modified Intent-to-Treat Analysis Set: The Modified Intent-to-Treat set consist of all participants who satisfy all the following:

  – Met all eligibility criteria and are enrolled in the study

- Received at least 1 dose of apalutamide
- Had a baseline PSA and at least 1 post-treatment PSA assessment.

This analysis set will be used for efficacy analyses of endpoints and subject disposition, unless otherwise specified.

5. STATISTICAL ANALYSES

5.1. General Considerations

Study Day will be calculated in reference to the date of first dose of study drug (apalutamide). Positive study days will count forward from Study Day 1. Study Day -1 will be the day before Study Day 1, and all subsequent negative study days will be measured backward from Study Day -1. There will be no Study Day 0.

The first dose starts on Day 1 of Cycle 1.

Unless otherwise specified, baseline value is defined as the closest measurement prior to the first dose of study drug. Change from baseline will be defined as (post-baseline value – baseline value).

Treatment Duration will be calculated as the duration of time from the date of the first dose of study drug (apalutamide) to the date of last dose of the study drug, i.e., date of last dose – date of first dose + 1.

Time to Event endpoints will be calculated as the number of days from the start of the study drug to the date of the event of interest, i.e., date of event of interest – date of first dose + 1. Time to event or duration of event endpoints will be based on the actual date of the event, not visit number or visit label. Confidence intervals of survival function at specific time point will be calculated using Kaplan-Meier method. In case no events have occurred by the given time point, a conservative approach will be used by assuming one event at the time point among subjects still at risk.

Continuous/numerical variables will be summarized using mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using count and percentage. In general, means and other measures of central tendency will be displayed with one more decimal digit than collected, and standard deviations and other measures of variability will be displayed with two decimal digits more than collected. For frequency counts of categorical variables, categories for which the counts are zero will be displayed for the sake of completeness. For example, if no subject discontinued due to “withdrawal of consent”, this reason would still be included in the table but with a count of 0.

5.1.1. Visit Windows

The reference day is Cycle 1 Day 1 of the treatment. A visit window of ±7 calendar days for visits 2 through 8 and a visit window of ±14 calendar days for visit 9 onwards for all follow-up visits are set up for this study.

5.2. Participant Dispositions

The number of participants in the following disposition categories will be summarized during treatment period using safety analysis set:

- Participants enrolled
- Participants who received study treatment
- Participants who completed the study
- Participants who discontinued study treatment
- Reasons for discontinuation of study treatment
- Participants who terminated study prematurely
- Reasons for termination of study

A listing of participants will be provided for the following categories:

- Participants who discontinued study treatment
- Participants who terminated study prematurely

5.3. Primary Endpoint(s) Analysis

The primary endpoint of the study is BCR-free rate at 24 months. BCR is defined as a confirmed PSA > 0.2 ng/mL.

BCR-free rate will be estimated from primary efficacy variable (time to BCR) using Kaplan-Meier method in modified intent-to-treat analysis set.

5.3.1. Definition of Endpoint(s)

Time to confirmed BCR will be defined as the time between the date of the first dose of study drug (apalutamide) and the date of the first occurrence of confirmed PSA > 0.2 ng/mL. Confirmation of PSA value will be done within 3-4 weeks regardless of study visit and timing. Depending on timing, this may be captured as an unscheduled visit.

Subjects without confirmed PSA > 0.2 ng/mL (including subjects who are lost-to-follow up) will be censored on their last PSA date during treatment phase of the study. Additional censoring rules are provided in 5.3.3.

The time to unconfirmed BCR (from the first dose of the study drug to the first occurrence of PSA > 0.2 ng/mL) will be used for sensitivity analysis of the primary endpoint using similar methodology.

5.3.2. Estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 4 components -

5.3.2.1. Population:

Subjects with high-risk localized or locally advanced prostate cancer who are treatment-naïve and have undergone RP for non-metastatic prostate cancer with post RP PSA ≤0.2 ng/mL

5.3.2.2. Variables:

- Time to confirmed BCR (confirmed PSA > 0.2 ng/mL).

5.3.2.3. Intercurrent Events and Strategies:

Table 1

Intercurrent Events (IE)	Strategy for Addressing IE	Description of Strategy	Data to be Included
Treatment discontinuation during treatment phase but continuing in the study.	Treatment Policy strategy	Occurrence of the IE is considered irrelevant in defining the treatment effect of interest	PSA value at the time of the primary analysis
Study withdrawal due to any reason, any time during the study (including treatment & study discontinuation during treatment phase)	While-on-Treatment strategy	Response to treatment prior to the occurrence of the IE is of interest	PSA value at the time of study withdrawal
Use of restricted and prohibited concomitant therapy any time during the study	While-on-Treatment strategy	Response to treatment prior to the occurrence of the IE is of interest	PSA value at the time of the start of restricted and prohibited concomitant therapy
Other protocol deviations	Treatment Policy strategy	Occurrence of the IE is considered irrelevant in defining the treatment effect of interest	PSA value at the time of the primary analysis
Death	While-Alive strategy	Response to treatment prior to the occurrence of the IE is of interest	PSA value at the time of death

5.3.2.4. Population level summary:

Time to confirmed BCR endpoint: Kaplan-Meier method will be used to estimate BCR-free rate at primary time point (24 months) along with 95% confidence interval.

5.3.3. Analysis Methods

The analysis of time to BCR will be performed at the end of study which is defined as the date of last participant's enrolment + 24 months or discontinuation of all study participants from the study, whichever occurs first. The distribution of time to BCR will be estimated using the Kaplan-Meier (KM) method. Median BCR-free time along with 90% confidence interval will be reported with Kaplan-Meier curve. The null hypothesis will be rejected if lower limit of the 90% confidence interval of KM estimate of BCR-free rate at 24 months is > 76%.

Time to unconfirmed BCR will be evaluated using same methodology as sensitivity analysis.

Modified ITT analysis set will be used for the analysis. Subjects with no evidence of BCR will be censored based on following rule:

- If the subject does not have baseline PSA measurement, the subject will be censored on the date of enrollment (Study Day 1)
- If the subject does not have confirmed PSA >= 0.2 ng/mL, the subject will be censored on the date of the last PSA measurement
- If the subject receives a protocol specified prohibited or restricted therapy, PSA measurements on or after such therapy will not be included in the analysis

These censoring rules will be applied appropriately to all intercurrent events in the trial as defined in Table 1. The details are as specified in Table 2.

Table 2: Censoring Rules to be used for intercurrent events

Intercurrent Event (IE) / EOS	Censoring (if no event, before the IE)	Assumption
IE: Study withdrawal due to any reason, any time during the study	PSA value censored at study withdrawal	Non-informative censoring as per censoring rule
IE: Use of restricted and prohibited concomitant therapy any time during the study	PSA value censored at the last PSA assessment prior to the time of the start of restricted and prohibited concomitant therapy	Non-informative censoring as per censoring rule

IE: Death	PSA value censored at the last PSA assessment prior to the time of death	Non-informative censoring as per censoring rule
End of study	(Administratively) censored at the last PSA assessment prior to the end of the study	Non-informative censoring as per censoring rule

5.4. Secondary Endpoint(s) Analysis

- BCR-free rate at 12 months
- Testosterone recovery rate at 18 and 24 months. Serum testosterone ≥150 ng/dL is defined as testosterone recovery.

5.4.1. Analysis Methods

Analyses of secondary efficacy endpoints will be performed using the methods similar to those for the primary endpoint using modified intent-to-treat analysis set.

Time to testosterone recovery will be analyzed using Kaplan-Meier (KM) method. Quartiles of the distribution along with 95% CI will be estimated. Estimates of testosterone recovery rates at 13-, 18-, and 24-month together with 95% CI will be estimated. Primary analysis censoring rule (5.3.3) as it relates to testosterone, will be used for these analyses.

5.5. Exploratory Endpoint(s) Analysis

- Incidence of rash

5.5.1. Analysis Methods

Rash is an AE of clinical interest to be assessed by NCI-CTCAE Version 5.0 criteria. Incidence of rash will be summarized descriptively using safety analysis set. Incidence rates will be summarized with frequency and percentage by system organ class (SOC) and preferred term (PT), with all subjects treated with study drug as the denominator. In addition, incidence rate will also be summarized by severity and relationship to the study drug.

5.6. Safety Analyses

The safety parameters to be evaluated are the incidence, intensity, and type of adverse events (AE), vital signs, ECG, and clinical laboratory results.

5.6.1. Extent of Exposure

Treatment duration (in terms of cycles and in months) will be defined as the duration from the date of the first dose of study drug to the date of last dose of study drug. Descriptive summary

statistics for duration of apalutamide treatment (N, mean, SD, median, and range (minimum, maximum)) will be summarized using safety analysis set.

Treatment duration will be calculated as the number of days with dosing record divided by 28 (i.e., expected number of days in a cycle) and 30.4375 (i.e., number of days in a month calculated as 365.25/12).

5.6.2. Adverse Events

Subjects will be assessed for adverse events at each clinic visit (as specified in protocol Schedule of activities) while on the study. Adverse events (AEs) will be graded according to the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 (published on 27 November 2017) and coded to preferred term and system organ class (SOC) using the MedDRA version 20.0 or later.

All AEs reported on or after the date of first dose until 30 days (inclusive) after the last dose of study drug will be considered treatment-emergent and will be summarized.

AE incidence rates will be summarized with frequency and percentage by SOC and preferred term, with all subjects treated as the denominator, unless otherwise specified. In addition, AE incidence rates will also be summarized by severity and relationship to study drug. Treatment-related AEs are those judged by the Investigator to be at least possibly related to the study drug. AEs with missing severity or relationship to study drug will be classified as severe and treatment-related, respectively. Subjects with multiple occurrences of events will only be counted once at the maximum severity to study drug for each preferred team, SOC, and overall. Deaths that occur within 30 days after the last dose of study drug are defined as on-study deaths.

Summary tables of the following AEs will be provided:

- Overall summary of AEs: the number and percentage of subjects who experienced any AE, number of subjects with Grade 3/4 AEs, any serious adverse event (SAE), any treatment- related AE, treatment related Grade 3/4 AE, any treatment-related SAE, AE leading to treatment discontinuation, related AE leading to treatment discontinuation, AE leading to death, related AE leading to death, and all deaths within 30 days of last dose
- All AEs by SOC and preferred term
- Most frequent AEs by SOC and preferred term (reported in ≥ 5% of subjects in either the investigational or control group)
- All AEs by SOC, preferred term, and toxicity grade
- Grades 3 or 4 AEs by SOC and preferred term
- Grades 3 or 4 AEs by decreasing frequency of preferred term
- Treatment-related AEs by SOC and preferred term
- Treatment-related AEs by SOC, preferred term, and toxicity grade
- Treatment-related AEs by decreasing frequency of preferred term

- Treatment-related Grades 3 or 4 AEs by SOC and preferred term
- Most frequent treatment-related Grades 3 and 4 AEs (reported in ≥ 5% of subjects in either the investigational or control group)
- Treatment-related Grades 3 or 4 AEs by decreasing frequency of preferred term
- All AEs that led to death by SOC and preferred term
- All AEs that led to study drug discontinuation by SOC and preferred term. Study drug discontinuation will be determined from the End of Treatment CRF (where reason for termination is "Adverse Event") and the specific AE will be determined from the AE eCRF page (where action taken is "Withdrawn from Study")
- All AEs that led to study drug discontinuation by SOC, preferred term, and toxicity grade
- All AEs that lead to study drug dose modification by SOC and preferred term
- All SAEs by SOC and preferred term
- All SAEs by SOC, preferred term, and toxicity grade
- Deaths by time period (Treatment Phase, Follow-up Phase) and cause of death

Subject listings of all Grades 3 or 4 AEs, all SAEs, AEs that led to study drug discontinuation, dose modification, and all deaths will be provided as well. If there are any AEs attributed to RP (e.g. lymphocele, intraoperative bleeding, postoperative bleeding, urinary incontinence), listings of all AEs (or relevant tables if there is a large of proportion of these subjects) will also be provided.

Narratives will be written for the following subjects in the final clinical study report:

- Subjects who die due to treatment-related adverse events ≤ 30 days after the last dose of study drug
- Subjects who discontinue study drug due to adverse events
- Subjects who have a treatment-related serious adverse event
- Subjects who experience a seizure

Subjects who experience other Grade 3 or higher treatment-emergent adverse events of special interest.

5.6.3. Additional Safety Assessments (if applicable)

5.6.3.1. Clinical Laboratory Tests

Study-specified laboratory assessments will be done only for PSA and testosterone (performed by local laboratory). Descriptive summary statistics of changes from baseline will be summarized at each scheduled time point.

5.6.3.2. Vital Signs and Physical Examination Findings

N/A

5.6.3.3. Electrocardiogram

Electrocardiograms (ECGs) (12-lead) will be recorded at Screening. Abnormalities noted at screening will be included in the medical history.

5.7. Other Analyses

5.7.1. Pharmacokinetics

N/A

5.7.2. Immunogenicity

N/A

5.7.3. Pharmacodynamics

N/A

5.7.4. Pharmacokinetic/Pharmacodynamic Relationships

N/A

5.7.5. Biomarkers

N/A

5.7.6. Health Economics

N/A

5.7.7. Other Variables and/or Parameters

N/A

5.7.8. Definition of Subgroups

Consistency of apalutamide treatment effect will be evaluated across different subject subpopulations. Subgroup analyses for time to BCR and testosterone recovery endpoints will be conducted, contingent on the number of events, and will consider the following baseline characteristics.

- Age
- Baseline ECOG PS grade
- Baseline Gleason score categories
- Baseline Tumor stage (T; N)

5.8. Interim Analyses

No interim analysis is planned for this study.

5.8.1. Data Monitoring Committee (DMC) or Other Review Board

No independent data monitoring committee (IDMC) is planned for this study.

A Steering Committee will be established to provide guidance and supervision for the study. The committee chair will have medical expertise in the relevant therapeutic area.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

The list below will be updated as appropriate

ADT	androgen deprivation therapy
AE	adverse event
CI	confidence interval
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
ECG	electrocardiogram
eCRF	electronic case report form
IQ	interquartile
IVRS	interactive voice response system
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic(s)
PP	per protocol
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SMQs	standardized MedDRA queries
TEAE	treatment-emergent adverse event
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

To be updated as necessary and will be finalized before data base lock.

6.3. Appendix 3 Demographics and Baseline Characteristics

The following parameters will be summarized using modified intent-to-treat analysis set:

- Age, race, ethnicity, weight, height
- Baseline ECOG PS grade

- All classifications of Gleason score
- Tumor stage (T; N)
- Baseline value of PSA, testosterone

6.4. Appendix 4 Protocol Deviations

Protocol deviations will be summarized using modified intent-to-treat analysis set. Protocol deviations will be reviewed on a case-by-case basis and major protocol deviations will be identified and summarized by the following example categories:

- Deviation from inclusion/exclusion criteria that may affect efficacy endpoints
- Administration of prohibited concomitant medication during the course of the study treatment period
- Received disallowed concomitant treatments
- Met withdrawal criteria but was not withdrawn
- Any other deviation that impacts subject safety

The categories will be finalized prior to database lock.

6.5. Appendix 5 Prior and Concomitant Medications

Prior and concomitant medications will be summarized using World Health Organization (WHO) Drug therapeutic class, and generic medication name using the safety analysis set. Prior medications are those taken (with medication start date) prior to Cycle 1 Day 1. Concomitant medications are those, other than study medication, taken during the Treatment Phase, i.e., with medication start date on or prior to the End-of-Treatment visit and medication stop date on or after Cycle 1 Day 1 or ongoing.

Subsequent prostate cancer therapies received after the Treatment Phase will be summarized by treatment group using the safety analysis set. If the therapy is medication, then it will also be summarized by WHO Drug therapeutic class and generic medication name.

6.6. Appendix 6 Medical History

Ongoing general medical history will be summarized by system organ class and preferred term using the safety analysis set.

6.7. Appendix 7 Intervention Compliance

Treatment compliance and dose modifications will be summarized using the safety analysis set.

Percent treatment compliance will be defined as the number of tablets taken during the study divided by the expected number of tablets, multiplied by 100. The number of tablets taken will be calculated based on the number of tablets dispensed minus the number of returned tablets. A

subject's expected number of tablets will be calculated according to the planned treatment regimen. For example, for subjects with no dose modification the expected number of tablets equals the number of assigned tablets per day multiplied by treatment duration (defined in Section 5.6.1), however for subjects with dose reduction the expected number of tablets will be smaller. Subjects with at least one dose modification or with dose interruption and the reason for the dose modification will be summarized by treatment group. ADT is background therapy and its dosing and modifications will be summarized by treatment group.

6.8. Appendix 8 Adverse Events of Special Interest

No non-serious AEs of special interest has been identified in this study.

Rash is an AE of clinical interest to be assessed by CTCAE criteria and following the specific rash management plan in protocol (Appendix 9, Recommendations for Management of Drug-related Rash).

6.9. Appendix 9 Medications of Special Interest

No concomitant medications of special interest have been identified in this study. Prohibited concomitant medications (listed in Appendix 6 of protocol) will be summarized using World Health Organization (WHO) Drug therapeutic class, and generic medication name using the safety analysis set.

6.10. Appendix 10 Laboratory Toxicity Grading

The grading scale to be used for lab assessments will be based on 'Common Terminology Criteria for Adverse Events (CTCAE Version 5.0) (3).

If a laboratory value falls within the grading as specified below but also within the local laboratory normal limits, the value is considered to be normal and will be reset to grade 0.

Pre-baseline measurements will use the same grading ranges as applied to baseline measurements. In case a test has two sets of ranges – one for baseline normal and one for baseline abnormal, the one for baseline normal will be applied for all measurements taken pre-baseline and on baseline.

7. REFERENCES

1. Martini, A., et al., Defining the Most Informative Intermediate Clinical Endpoints for Predicting Overall Survival in Patients Treated with Radical Prostatectomy for High-risk Prostate Cancer. Eur Urol Oncol, 2019. 2(4): p. 456-463.
2. PASS 15 Power Analysis and Sample Size Software (2017). NCSS, LLC. Kaysville, Utah, USA. Available at https://www.ncss.com/software/pass. Accessed November 2019.
3. Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0; Published: November 27, 2017