# STATISTICAL ANALYSIS PLAN

Final Version 2.0, dated 16-OCT-2020

# A Randomized Study of Enzalutamide in Subjects with Localized Prostate Cancer Undergoing Active Surveillance (ENACT)

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# I. LIST OF ABBREVIATIONS AND KEY TERMS

**List of Abbreviations**

| Abbreviations | Description of abbreviations |
|---|---|
| AE | Adverse Event |
| ADT | Androgen Deprivation Therapy |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| AR | Androgen Receptor |
| AS | Active Surveillance |
| AST | Aspartate Aminotransferase |
| BFI | Brief Fatigue Index |
| BMI | Body Mass Index |
| CBC | Complete Blood Count |
| CSR | Clinical Study Report |
| CT | Computerized Tomography |
| DHT | Dihydrotestosterone |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| EPIC | Expanded Prostate Cancer Index Composite |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| GS | Gleason Score |
| IRT | Integrated Response Technology |
| ISN | International Study Number |
| LS | Least Square |
| MAX-PC | Memorial Anxiety Scale for Prostate Cancer |
| MedDRA | Medical Dictionary for Regulatory Authorities |
| MiPS | Michigan Prostate Score |
| MMRM | Mixed Model Repeated Measures |
| mpMRI | Multiparametric Magnetic Resonance Imaging |
| MRI | Magnetic Resonance Imaging |
| MUGA | Multi Gated Acquisition Scan |
| NCCN | National Comprehensive Cancer Network |
| NCI-CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| PD | Protocol Deviation |
| PPS | Per Protocol Set |
| PSA | Prostate Specific Antigen |
| QOL | Quality of Life |
| SAE | Serious Adverse Event |
| SAF | Safety Analysis Set |
| SAP | Statistical Analysis Plan |
| SEER | Surveillance, Epidemiology and End Results |
| SF-12 | Medical Outcomes Study 12-Item Short Form Survey |
| TEAE | Treatment-Emergent Adverse Event |

| Abbreviations | Description of abbreviations |
|---|---|
| TLFs | Tables, Listings and Figures |
| TRUS | Transrectal Ultrasonography |
| ULN | Upper Limit of Normal |
| WHO | World Health Organization |

# 1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data.

The SAP is finalized and signed prior to any of the following: study unblinding, database hard lock, interim analysis, or accumulation of a substantial amount of data to ensure lack of bias. If needed, revisions to the approved SAP may be made prior to database hard lock. Revisions will be version controlled.

This statistical analysis is coordinated by the responsible biostatistician of Astellas Pharma US, Medical Affairs, Americas. Any changes from the analyses planned in the SAP will be justified in the Clinical Study Report (CSR).

Prior to database hard lock, a final review meeting of data and tables, listings, and figures (TLFs) will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database hard lock.

## 1.1 Background

Prostate cancer is the most commonly diagnosed cancer (other than skin cancer) among men. In 2015 the American Cancer Society estimates that 220,800 men will develop prostate cancer in the United States and about 27,540 will die of prostate cancer (American Cancer Society, 2015). Of those diagnosed, 80% will be diagnosed with localized disease according to Surveillance, Epidemiology and End Results (SEER) data (SEER 18 2005-2011). For localized disease, there are multiple options – active surveillance (AS), radical prostatectomy and external beam radiotherapy / brachytherapy (NCCN, 2015). Interventional options, however, carry risks. Radical prostatectomy (open or robotic) has long term risks of erectile dysfunction and urinary incontinence. External beam radiation therapy and brachytherapy also carry risks, such as erectile dysfunction, urinary incontinence and bowel complications. AS has emerged as one of the recommended options for localized prostate cancer (Mohler et al, 2010; Thompson et al, 2007). AS use is increasing for low risk disease over the years 2010-2013 compared to the years before then (Cooperberg & Carroll, 2015; Ritch et al, 2015; Weiner et al, 2015). Ritch et al (2015) also noted increasing use of observation for low risk prostate cancer in an analysis of the SEER-Medicare database. This increase in AS is mostly due to concern that clinically low risk prostate cancer is over-treated, and AS may reduce unnecessary treatment in these subjects. (Lane et al, 2014; Wilt, 2014; Wilt et al, 2012; Bill-Axelson et al, 2011). AS studies have also included men with higher risk features including Gleason pattern 4 (Klotz et al, 2015; Cooperberg et al, 2011).

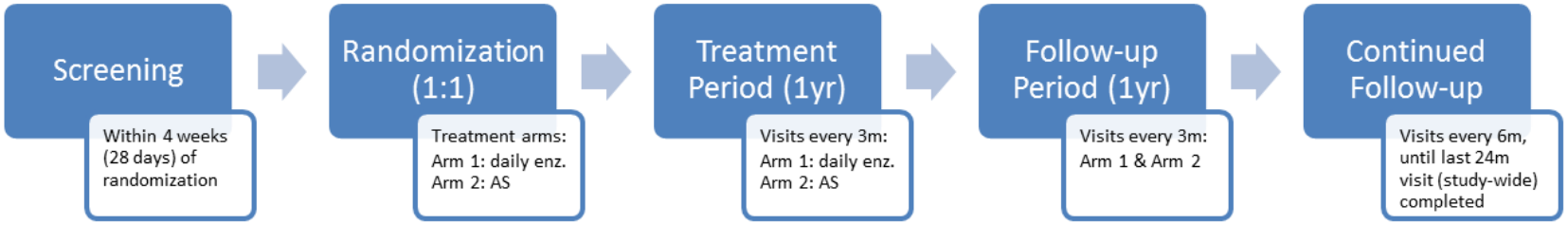
Subjects who progress on AS are at risk for sequelae of their prostate cancer and often receive interventions which carry significant risks and side effects. To date, no studies have been published with an intervention of a known anti-cancer agent in an AS population.

Because of this, novel approaches are needed to both stratify and offer options for those on AS as well as to offer an intervention that might affect progression. Also, current AS groups

encompass different subject populations. Some populations with certain characteristics (related to medical or family history or [redacted] might progress more often on AS than other populations. This study will allow us to examine these issues, as well as to examine any effect of enzalutamide on these different subsets of subjects. The use of enzalutamide monotherapy will potentially allow for optimal tumor treatment without the side effects and effects on quality of life inherent to androgen deprivation therapy (ADT).

# 2 FLOW CHART AND VISIT SCHEDULE

**Figure 1 Flow Chart**




Abbreviations: AS = active surveillance, enz. = enzalutamide (160 mg PO daily), yr = year, m = months

**Table 2 Schedule of Assessments**

| Study Visit Name | Screening | Randomization | 3m | 6m | 9m | 12m | 15m | 18m | 21m | 24m | >24m, q6m[1] | Unscheduled[2] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **-28 to -7** | **1** | **85** | **176** | **267** | **358** | **455** | **545** | **635** | **730** | **>730** | **n/a** |
| **Week** | **-4 to -1** | **1** | **13** | **26** | **39** | **52** | **65** | **78** | **91** | **104** | **>104** | **n/a** |
| **Window (days)** | | | ± 7 | ± 7 | ± 7 | ± 7 | +7 | +7 | +7 | +7 | ± 7 | **n/a** |
| | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | |
| Medical History[3] | X | X[3] | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | X | | | | | | | | | | |
| Randomization | | X | | | | | | | | | | |
| Vital Signs | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical Examination, Weight[4] | X | | X | X | X | X | X | X | X | X | X | X |
| 12-Lead ECG | X[5] | | | | | | | | | | | |
| MUGA/Echocardiogram[6] | X[5] | | | | | | | | | | | |
| Clinical Labs[7] | X | X | X | X | X | X | X | X | X | X | X | X |
| Serum hormone levels[8] | | X | | | | X | | | | X | | X |
| Serum PSA[9] | X | X | X | X | X | X | X | X | X | X | X | X[10] |
| Digital Rectal Examination | X | | | X | | X | | X | | X | X | X[10] |
| [redacted] | [redacted] | | | [redacted] | | [redacted] | | [redacted] | | [redacted] | [redacted] | |
| Transrectal ultrasound-guided prostate biopsy(12 core)[12] | X[13] | | | | | X | | | | X | | X[10] |
| BFI[14] | | X | X | X | | X | | X | | X | | |
| SF-12[14] | | X | | X | | X | | X | | X | | |
| EPIC[14, 15] | | X | | X | | X | | X | | X | | |
| MAX-PC[14] | | X | | X | | X | | X | | X | | |
| Adverse Events[16] | | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X | X |
| Therapies and Outcomes Review | | X | X | X | X | X | X | X | X | X | X | X |
| Study Drug Dispensing[17] | | X | X | X | X | X | | | | | | |
| Blood Sample for Potential Future Analysis(optional)[18] | | X | X | X | X | X | X | X | X | X | X | X |

1. Subjects will be followed every 6 months until the last subject (study-wide) has completed the 24m Visit.
2. Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events (AEs), at the subject's request or if deemed necessary by the investigator.
3. Medical history will include capturing information about any first degree relatives with prostate cancer. Any updates to the subject's medical history will be recorded at the Randomization Visit (Study Day 1) prior to randomization.
4. A complete physical examination will be completed at the Screening Visit. For all visits after the Randomization visit, only a brief physical examination is required.
5. This procedure (if required) must be done within 28 days prior to randomization.
6. A multi-gated acquisition (MUGA) scan or echocardiogram is only required if the subject has a history of anthracycline or anthracenedione (mitoxantrone) treatment.
7. Clinical labs, which will be assessed by the study's central laboratory, include serum chemistries (comprehensive metabolic panel) and hematology (CBC with differential).
8. Serum hormonal levels to be measured are testosterone, DHT, dihydroepiandrosterone, androstenedione and estradiol.
9. Serum PSA will be measured by the study's central laboratory.
10. If warranted per Investigator's clinical opinion or per standard of care.
11. [redacted]CCI[redacted].
12. Biopsies may be done with or without mpMRI targeting. Sites must use a consistent method (either with or without mpMRI targeting) for all of their study subjects. Any biopsy performed during the subject's study participation will be analyzed centrally (for histological reading, [redacted]CCI[redacted].
13. Biopsy must be done within 6 months prior to the Screening Visit, and submitted for central analysis (histological reading, [redacted]CCI[redacted]. For this biopsy, a minimum of 10 cores is required.
14. Subjects who withdraw from the study prior to the 24m Visit will be asked to complete all subject reported outcomes questionnaires (BFI, SF-12, EPIC, MAX-PC) at their final study visit.
15. Only the urinary, sexual and hormonal domains will be used.
16. Adverse events (serious and non-serious) will be collected from the time the subject signs the consent form until the subject completes the study.
17. Study drug is only applicable to subjects randomized to the enzalutamide arm; subjects randomized to AS will not be dispensed any study drug.
18. Subjects will have the option of having an additional sample collected at each phlebotomy session for storage and analysis in future trials of future trials of biomarker discovery for localized prostate cancer

# 3 STUDY OBJECTIVE(S) AND DESIGN

## 3.1 Study Objective(s)

The primary objective is to compare the time to prostate cancer progression (pathological or therapeutic progression) between subjects treated with enzalutamide versus subjects undergoing active surveillance.

The secondary objectives are to evaluate:

- Safety
- Proportion of subjects with negative biopsy for cancer at 1 year and 2 years
- Percent of cancer positive cores at 1 year and 2 years
- Time to PSA progression (secondary rise in serum PSA≥25% above baseline or ≥25% above nadir or absolute increase ≥ 2 ng/mL)
- Proportion of subjects with secondary rise in serum PSA≥25% above baseline or ≥25% above nadir or absolute increase ≥ 2 ng/mL at 1 year and 2 years
- Brief fatigue index (BFI)
- Medical outcomes study 12-item short form survey (SF-12)
- Expanded Prostate Cancer Index Composite (EPIC) questionnaire- urinary, sexual and hormonal domains
- Memorial Anxiety Scale for Prostate Cancer (MAX-PC) questionnaire

[redacted] CCI

[redacted]

## 3.2 Study Design

This is a multicenter, randomized, open label exploratory study, conducted in the US and Canada, evaluating the efficacy and safety of enzalutamide for extension of time to prostate cancer progression (pathological or therapeutic) in subjects with clinically localized, histologically proven prostate cancer that is categorized as low risk or intermediate risk and who are under AS. A total of 222 subjects from approximately 50 centers will be enrolled. Subjects are eligible if they were diagnosed within 6 months of screening and have been on AS. A minimum of ten cores from transrectal ultrasound-guided prostate biopsy (mpMRI targeted versus non-mpMRI targeted) are required; confirmatory biopsy before entering the study is not required and is done at the discretion of the investigator.

Low risk is defined as T1c-T2a, PSA<10, N0, M0 (or presumed N0, M0 if computerized tomography [CT]/bone scan not done due to low risk of metastases), GS ≤ 6, ECOG status ≤2 and estimated life expectancy >5 years. Intermediate risk is defined as T2b-T2c, PSA<20, N0, M0 (or presumed N0, M0 if CT/bone scan not done), GS ≤7 (3+4 pattern only), ECOG status ≤2 and estimated life expectancy > 5 years.

Prostate cancer progression is defined as either therapeutic progression or pathological progression. Therapeutic progression is defined as the earliest occurrence of primary therapy for prostate cancer (prostatectomy / radiation / focal therapy / systemic therapy). Pathological progression is defined as increase in primary or secondary Gleason pattern by > 1 or higher

proportion of cancer positive cores (>15% increase). Subjects will be stratified by low versus intermediate risk and type of biopsy performed (mpMRI targeted versus non-mpMRI targeted).

Subjects will be randomized (1:1) either to receive treatment with enzalutamide (160 mg), administered as four 40 mg capsules, by mouth, once daily or to AS during the one year study treatment period. Following the one year treatment period, all subjects will be followed for one additional year. Subjects will be followed up every 3 months for these 2 years, after which follow-up will either be every 6 months or unscheduled until the last subject finished their 2 year follow-up. Serum PSA will be measured at baseline and every 3 months during subsequent follow-up visits.

Digital rectal examination will be done at baseline and every 6 months during subsequent follow-up visits. All subjects will have transrectal ultrasound-guided prostate biopsy (with or without mpMRI targeting) at 12 months and 24 months with a standard of 12 cores required; two biopsies are required from each target site (if mpMRI is used) as well as 12 systematic biopsies (12 core transrectal ultrasonography [TRUS] guided systematic biopsies including six lateral and six mid lobar cores from the base, middle and apex of the gland) at the same time. All sites will be consistent with their method of biopsy (with regards to the use of mpMRI targeting) throughout the study for all subjects enrolled at that site. If there is a significant clinical reason such as adverse changes on digital rectal examination or increase in PSA, biopsy is allowed based on investigator's decision. If at any time during the study the subject considers intervention for prostate cancer, biopsy is allowed and recommended.

Treatment decisions based on pathological progression are at the discretion of the individual investigator. Hormonal levels (testosterone, DHT, dihydroepiandrosterone, androstenedione and estradiol) will be collected at baseline, 12 months and 24 months. Quality of life/sexual function questionnaires (EPIC), anxiety measures (MAX-PC), BFI, SF-12 assessments will also be done at baseline, 6 months, 12 months, 18 months and 24 months. An additional BFI assessment will be done at 3 months. Subjects who withdraw from the study before the 24 Month visit will be asked to complete the EPIC, MAX-PC, BFI and SF-12 assessments at their final study visit.

Subjects will be followed beyond the two year study period until the last subject has completed the 24 month visit. This additional follow up will entail biannual visits (every 6 months and/or unscheduled visits) that include measurement of serum PSA and digital rectal exam.

All biopsy samples, including those collected for-cause or per standard of care, will be centrally read by a designated pathologist blinded to treatment allocation. CT, magnetic resonance imaging (MRI) and bone scan will be performed at the discretion of the investigator based on clinical need; when performed, these assessments will be read locally and recorded in the electronic case report form (eCRF).

Throughout the study, safety and tolerability will be assessed by the recording of AEs, monitoring of vital signs, physical examinations and safety laboratory evaluations.

A dose of 160 mg enzalutamide (four 40 mg capsules) once daily, administered orally, is the FDA approved daily dose for the indications in the approved labeling.

## 3.3 Randomization

Randomization will be performed on Study Day 1 via Interactive Response Technology (IRT). Prior to the initiation of the study treatment, the site staff will contact the IRT in order to determine the randomly assigned treatment. Specific procedures for randomization through the IRT are contained in the study procedures manual.

The randomization allocation will consist of 1:1 ratio for once daily enzalutamide or AS. The randomization will be stratified according to the following two factors:

- Low versus intermediate risk
- Type of biopsy performed (mpMRI targeted versus non-mpMRI targeted)

Additionally, enrollment of subjects with low risk prostate cancer will be capped to not exceed 80% of the study population.

# 4 SAMPLE SIZE

This study is designed to evaluate time to prostate cancer progression (pathological or therapeutic progression) as the primary endpoint. The overall two-sided type I error for this study is set at 0.05 level. The characteristics of time to prostate cancer progression (pathological or therapeutic progression) are used to determine the total sample size and overall duration.

A sample size of 222 subjects randomized in a 1 to 1 manner accrued over one year, a study duration of 3 years, loss-to follow-up of 16%, an assumed underlying hazard ratio of 0.52 and a three year median time-to-progression for the Control group (0.2310 rate) will result in 72 events (Fleshner et al., 2012). This sample size is sufficient to power this study at 80% with a two-sided type I error rate of 5%.

The assumed hazard ratio of 0.52 is consistent with Fleshner et al. (2012). Specifically, the Fleshner study is powered to detect a 39% failure rate reduction in the treated group with respect to a three year 45% failure rate in the control group. We used a more conservative 30% failure rate reduction for the treated group and a 50% three year failure rate for the control group. This resulted in parameter estimates of 0.2310 for the Control group and 0.1189 for the Treatment group, and thus, resulted in the hazard rate of 0.52.

# 5 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

Detailed criteria for analysis sets will be laid out in Classification Specifications (CS) and the allocation of subjects to analysis sets will be determined prior to database hard lock.

## 5.1 Full Analysis Set (FAS)

Full Analysis Set (FAS): This population includes all subjects who are randomized. This will be the primary analysis set for efficacy analyses.

## 5.2 Per Protocol Set (PPS)

Per Protocol Set (PPS): This population includes all subjects who adhere to the protocol, i.e. all subjects who were randomized and who did not have any protocol deviations.

The criteria used to define protocol deviations adheres to the International Conference of Harmonizations (ICH) definitions of protocol deviations and are defined in section 5.2.1. Final judgments on exclusion of subjects from PPS are to be made by the Astellas study team.

The PPS will be a secondary analysis set for efficacy. Selected baseline demographic and baseline characteristics may also be summarized for the PPS.

### 5.2.1 Reasons for Exclusion From PPS

All documented protocol deviations will be reviewed in the data review meeting prior to database lock. The following criteria listed in Table 3 may lead to subject's exclusion from PPS

**Table 3**

| ICH Category | ICH Definition | ENACT Interpretation |
|---|---|---|
| PD [1] | Subjects who entered the study even though they did not satisfy the entry criteria | • Subject randomized without meeting the inclusion/exclusion criteria<br>• Subject missed assessment(s)/procedure(s) impacting eligibility for study participation |
| PD [2] | Subjects who developed withdrawal criteria during the study but were not withdrawn | • Subject developed withdrawal criteria during the study and was not withdrawn |

| | | |
|---|---|---|
| PD [3] | Subjects who received the wrong or incorrect treatment dose | • Subject received wrong treatment or incorrect dose, or patient taking commercial Xtandi instead of study-labeled enzalutamide, also consuming drug that should have been quarantined |
| PD [4] | Subjects who received excluded concomitant treatment | • Subject took medication prohibited by the protocol |

## 5.3 Safety Analysis Set (SAF)

Safety Analysis Set (SAF): This population includes all subjects who enrolled in the study are randomized to receive study drug. Therefore, the SAF is equivalent to the FAS. This population will be used for analysis of safety data.

## 5.4 Pharmacokinetics Analysis Set (PKAS)

Not Applicable

## 5.5 Pharmacodynamic Analysis Set (PDAS)

Not Applicable

# 6 ANALYSIS VARIABLES

## 6.1 Efficacy Endpoints

### 6.1.1 Primary Efficacy Endpoint(s)

The primary endpoint is time to prostate cancer progression (pathological or therapeutic progression).

### 6.1.2 Secondary Efficacy Endpoints

The secondary endpoints are:

- Safety
    - Adverse events / treatment-emergent adverse events
    - Clinical laboratory variables (hematology, biochemistry including liver enzymes and total bilirubin)
    - Vital signs (systolic and diastolic blood pressure and pulse rate)
    - 12-lead electrocardiogram (ECG)
    - Physical examination assessments
- Incidence of negative biopsies for cancer at 1 year and 2 years
- Percent of cancer positive cores at 1 year and 2 years
- Time to PSA progression (secondary rise in serum PSA≥25% of baseline or≥25% above nadir or absolute increase ≥ 2ng/mL)
- Incidence of secondary rise in serum PSA≥25% baseline or ≥25% above nadir or absolute increase ≥ 2ng/mL at 1 year and 2 years
- BFI
- SF-12 assessments
- EPIC questionnaire (urinary, sexual and hormonal domains)
- MAX-PC questionnaire

### 6.1.3 [redacted]

CCI

[redacted]

- [redacted]
- [redacted]
- [redacted]

## 6.2 Pharmacokinetic Variables

Not Applicable

## 6.3 Pharmacodynamic Variables

Not Applicable

## 6.4 Other Variables

To clearly state, the following variables are defined:

- Month = 30.4375 days. Year = 365.25 days.
- BMI($kg/m^2$) = Weight(kg) / Height($m^2$)
- Age at randomization= floor((intck('month', birth date, randomization date) – (day(randomization date) < day(birth date)))/12
- Time since initial/histological diagnosis (years) = [(date informed consent signed - date of initial/histological diagnosis) + 1]/365.25.
- Time since initial diagnosis to Randomization (years) = [(date of Randomization – date of initial diagnosis) +1]/365.25.
- The duration of treatment was calculated as the (last dose date – first dose date) + 1.
- Number of pills taken from one visit to the next = number of pills dispensed – number of pills returned.
- Study drug compliance at each visit is calculated as = [(number of pills dispensed – number of pills returned) / (4 * number of days in the visit period)] * 100.
- Baseline results are defined as the last assessment prior to first dose of study drug, for subjects randomized to once daily enzalutamide. For subjects randomized to active surveillance, baseline is defined as the last assessment prior to or on the date of randomization.
- Treatment Emergent Adverse Events (TEAEs) are any AEs occurring on or after date of first study drug dose date (or randomization for AS) until 30 days post-treatment end date (or 1-year plus 30 days for AS).
- Treatment Phase is defined as date of first study drug dose (or randomization for AS) until either 30 days post treatment end date or (if earlier) study discontinuation date.
- 1-Year Follow-Up Phase is defined as 31 days post treatment end date until either completing 1-Year Follow-Up or (if earlier) study discontinuation date.
- Continued Follow-Up Phase is defined as the day after completing 1-Year Follow-Up phase until study discontinuation date.

Study Day is defined using the following step-wise function:

- If date of interest is on or following randomization, Study Day = Date of Interest – Randomization Date + 1;
- Else, Study Day = Date of Interest – Randomization Date.

Change from baseline is the difference between the result on a post baseline visit and baseline assessment.

Rise in serum PSA is defined as PSA ≥ 25% of baseline or ≥ 25% above nadir or absolute increase > 2ng/mL.

Progression-free survival is defined as the time (in months) from the date of randomization until the date of the cancer progression (pathological or therapeutic). Pathological progression is defined as increase in primary or secondary Gleason pattern by ≥ 1 or higher proportion of cancer positive cores (≥15% increase). Therapeutic progression is defined as the earliest occurrence of primary therapy for prostate cancer (prostatectomy/radiation/focal therapy/systemic therapy).

Subjects with no cancer progression at the time of trial completion (the last study-wide subject completes a 24 month follow-up visit), discontinuation or death will be censored at the last assessment date. Subjects discontinuing therapy will not be censored until the time of study discontinuation. Additionally, subjects switching therapy during the study will be censored at the time of the initial therapy switch.

For subjects on enzalutamide, TEAEs, defined as an adverse event observed after starting administration of the study drug and until 30 days after treatment end date, are categorized as AEs. If the adverse event occurs on Day 1 and the onset check box is marked "Onset after first dose of study drug" or the onset check box is left blank, then the adverse event will be considered treatment emergent. If the adverse event occurs on Day 1 and the onset check box is marked "Onset before first dose of study drug", then the adverse event will be categorized as medical history. If a subject experiences an event both during the pre-investigational period and during the investigational period, the event will be considered as an AE only if it has worsened in severity (i.e. it is reported with a new start date). All adverse events collected that begin within 30 days following study discontinuation will also be counted.

Percent positive cores are calculated using the number of systemically-sampled prostate regions and any targeted regions with at least one positive core divided by the total number of systematically-sampled regions and targeted regions. This implies that despite the number of samples within a given systematic or targeted region, any positive core will indicate that region as positive.

# 7 STATISTICAL METHODOLOGY

## 7.1 General Considerations

In general, descriptive statistics are defined for continuous variables as number of subjects (n), mean, standard deviation, minimum, median and maximum, and as frequency and percentage for categorical variables.

In summary and analysis tables of continuous variables, the minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean, median, quartile, and 2-sided 95% confidence interval (CI) will be presented to 1 more decimal place than the original data. The standard deviation and standard error will be presented to 2 more decimal places than the original data.

In summary tables of categorical variables, the number of non-missing observations and percentages will be presented. Unless specified otherwise, percentages by categories will be based on the number of subjects with no missing data. For categorical variables with missing values, an additional level of the variable will be added to the summary as "Missing" and the frequency will be displayed but no percentage.

Efficacy analysis will be conducted on the FAS and PPS. The primary analysis set for efficacy analyses will be the FAS. The PPS will be used to assess the robustness of the results from the statistical tests based on the FAS. Summaries based on FAS and PPS will be presented by planned treatment group, unless specifically stated otherwise. Safety analysis and other summaries based on SAF will be presented by actual treatment received.

Unless otherwise specified, all statistical testing will be conducted using two-sided tests with a significance level of 0.05.

All statistical analyses will be performed using SAS® v9.3 or higher. Specifications for table, figures, and data listing formats can be found in the TLF specifications for this study.

For the definition of subgroups of interest please refer to section 7.8.

## 7.2 Study Population

### 7.2.1 Disposition of Subjects

The following subject data will be presented:

- Number of subjects with informed consent, discontinued before randomization, randomized (overall only);
- Number of subjects randomized in each analysis set, by treatment group and overall;
- Number and percentage of subjects that received study drug, by treatment group and overall;
- Number and percentage of subjects completed and discontinued treatment, by primary reason for treatment discontinuation for randomized subjects, by treatment group;
- Number and percentage of subjects completed and discontinued the 1 year follow-up period, by primary reason for discontinuation, by treatment group and overall;
- Number and percentage of subjects completed and discontinued the continued follow-up period, by primary reason for discontinuation, by treatment group and overall;
- Number and percentage of subjects excluded from PPS by reason for exclusion defined in section 5.2.1, by treatment group and overall.

### 7.2.2 Protocol Deviations

Protocol deviations will be reported in data listing(s) by site, treatment group and subject. And will be presented by Syneos Health no later than the data review meeting (DRM) in order to adjudicate deviations prior to database lock. All protocol deviations will be reviewed and categorized prior to the database lock. A major deviation has an impact on subject safety, may substantially alter risks to subjects, may have an effect on the integrity of the study data, or may affect the subject's willingness to participate in the study. A minor deviation is a minor or administrative departure from the protocol without prior consent and does not have an impact on subject safety, nor an effect on the integrity of the study data.

### 7.2.3 Demographic and Other Baseline Characteristics

Demographic data (age, sex, race, and ethnicity) will be summarized by treatment group and overall for the FAS. Descriptive statistics will be included for continuous endpoints and frequency and percentage for categorical endpoints.

Subject characteristics of height (in cm), weight (in kg), BMI at screening, substance use/tobacco history, 12-lead electrocardiogram interpretations, biopsy targeting method (mpMRI vs non-mpMRI), prostate cancer risk group (low vs. intermediate) and the incidence of relatives with prostate cancer and their age at diagnosis will be summarized with descriptive statistics by treatment group and overall for the FAS.

Data listings will be presented for the demographic and baseline characteristic data.

### 7.2.4 Previous and Concomitant Medications

Prior and concomitant medications will be coded according to the World Health Organization (WHO) DDE version March 2016. Prior medications are non-study medications that are recorded and stopped prior to the screening visit date. Prior medications will be exclusively reported in data listings. Concomitant medications are those that start on or after the screening visit date. Non-medication therapies will not be coded and summaries will be limited to overall use, reason for use, and radiation details.

Concomitant medications will be summarized descriptively for each treatment group and overall by therapeutic subgroup (ATC 2nd level), chemical subgroup (ATC 4th level) and preferred name by treatment group for the FAS and displayed in data listings. Subjects taking the same medication multiple times will be counted once per medication and investigational period. A medication that can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups.

### 7.2.5 Medical and Disease Histories

Medical history including cancer (disease history), non-cancer history, and prior surgical procedures will be summarized by treatment group and overall for the FAS and coded using the Version 23.0 of the Medical Dictionary for Regulatory Activities (MedDRA) to system organ class and preferred term. The dictionary will up version once every two years pending sponsor decision. If a subject experienced more than one medical condition within a system organ class, the subject will be counted once under that system organ class. If a subject had more than one count for a particular preferred term, the subject will be counted once under that preferred term.

Disease history data of time since initial diagnosis, time since histological diagnosis and incidence of Primary Gleason Pattern (at initial diagnosis), Secondary Gleason Pattern (at initial diagnosis), Total Gleason Score (at initial diagnosis), Clinical Tumor Stage (at initial diagnosis), Clinical Lymph Node Stage (at initial diagnosis), distant metastasis, prostate cancer-related biomarker testing done (from time of diagnosis until screening) will be summarized by descriptive statistics by treatment group and overall for the FAS.

Data listings will be presented for the medical and surgical histories and disease history.

## 7.3 Study Drugs

### 7.3.1 Exposure

Active treatment for prostate cancer and type of therapies will be assessed at Randomization and every study visit thereafter until month 24 and unscheduled. The following information will be presented by treatment group for the FAS:

- Descriptive statistics for cumulative amount of drug that a subject was exposed, and
- Number and percent of subjects with dose decreases, increases or interruptions by treatment group.

Duration of exposure will be summarized in two ways by treatment group.

- Descriptive statistics for days on therapy.
- Frequencies and percentages of exposure time (in days) as follows:
    - less than 7 days
    - at least 7 days, less than 14 days
    - at least 14 days, less than 28 days
    - at least 28 days, less than 42 days
    - 42 days or more
    - Unknown.

### 7.3.2 Treatment Compliance

The study treatment administration and compliance profile will be summarized descriptively for each visit and overall for the SAF and displayed in data listings. Summaries for number of pills dispensed during a visit and number of pills taken (number of pills dispensed – returned) will be displayed. Compliance (%) for a particular visit will be calculated as: [(number of pills dispensed – number of pills returned) / (4 * number of days in the visit period)] * 100.

Percent overall compliance will be summarized in two ways for the SAF:

- Descriptive statistics will be presented by treatment group.
- Percent compliance will be categorized according to the following categories by treatment group:
    - less than 50%
    - at least 50%, less or equal to 75%
    - greater than 75%
    - Unknown.

## 7.4 Analysis of Efficacy

All efficacy analyses will be performed on the FAS and PPS.

### 7.4.1 Analysis of Primary Endpoint(s)

The primary efficacy endpoint is time to prostate cancer progression (pathological or therapeutic), and the hypothesis for analysis is:

$H_0$: The time to progression for Enzalutamide and Active Surveillance (AS) are the same $H_1$: The time to progression for Enzalutamide and AS are not the same

Median and 95% confidence intervals for time to prostate cancer progression (pathological or therapeutic) will be calculated with the Kaplan-Meier (KM) method for each treatment group. Subjects with no cancer progression at the time of trial completion, discontinuation or death will be censored at the last assessment date. Additionally, subjects switching therapy during the study will be censored at the time of the initial therapy switch, but subjects discontinuing therapy will not be censored until the time of study discontinuation. If less than 50% of subjects progress by study cut-off time, the 25th percentile and its two-sided 95% confidence interval will be reported. KM plots will be generated.

Treatment group differences between enzalutamide versus AS will be based on a Cox regression model. The resulting Hazard ratio (enzalutamide/AS) and 95% confidence interval will be included in the summary. Censoring assumptions will follow the same rules as applied for the KM estimates. Fixed effects for the model will include the treatment groups, randomization stratification factors [prostate cancer risk (low/intermediate), type of biopsy performed (mpMRI targeted/non mpMRI targeted)], age, race, and time since prostate cancer diagnosis. Additionally, a random effect of site will be included in the model.

The association between the survival time, log of time to disease progression, and survival probability, log negative log, will be investigated graphically by Cox proportional-hazards models. If the proportional hazards assumption is violated, appropriate remedial methods will be investigated and applied.

Data listings will be provided.

In addition to an overall analysis, the primary and secondary analyses will be repeated for pathological progression and therapeutic progression, individually.

#### 7.4.1.1 Secondary Analyses

The incidence of subjects with prostate cancer progression (pathological or therapeutic) will be summarized with frequencies and percentages at one year, two years, and study completion. Treatment group differences will be assessed using a logistic regression with the same covariates and random effect used in the primary analysis and include two-sided 95% confidence interval estimates of the odds ratio.

In addition to an overall analysis, the primary and secondary analyses will be repeated for pathological progression and therapeutic progression, individually.

#### 7.4.1.2 Subgroup Analysis

Subgroup analyses of time to progression will be performed to evaluate the treatment effect based on the following subgroups: age (<65, 65 to <75, and >=75), race, and BMI at screening

(<25; 25-30; and >30). Kaplan-Meier methods, Cox regression models and censoring rules described in section 7.4.1 will be used for each analysis. Summary tables will be presented.

#### 7.4.1.3 Stratification Factors

Analyses of time to progression will include randomization stratification factors to evaluate their effects. These factors are prostate cancer risk (low and intermediate) and type of biopsy performed (mpMRI targeted and non-mpMRI targeted).

### 7.4.2 Analysis of Secondary Endpoints

#### 7.4.2.1 Cancer Biopsy Incidence and Secondary Rise in PSA

The incidence of negative biopsy for cancer and secondary rise in serum PSA will be summarized with frequencies and percentages at one and two years by treatment group, subgroups and overall.

Treatment comparisons will be performed using the exact binomial distribution as well as the normal approximation to the binomial distribution. Inferences will include 95% confidence intervals of the odds ratio for each endpoint between treatment groups at both Year 1 and Year 2 for biopsies and for each of Years 1 and 2 and end of study for PSA. Comparison between enzalutamide and AS will be evaluated by logistic regression using the treatment groups, randomization stratification factors [prostate cancer risk (low/intermediate), type of biopsy performed (mpMRI targeted/non mpMRI targeted)], age, race, and time since prostate cancer diagnosis as fixed effects and site and subject as random effects.

Time to PSA progression will be analyzed with the same methods as detailed for the primary endpoint analysis in Section 7.4.1.

#### 7.4.2.2 Brief Fatigue Inventory

The Brief Fatigue Inventory (BFI) is a questionnaire that assesses tiredness, fatigue, ability to perform general activities, mood, walking ability, interaction with others, etc. using 9 questions, assessed at Randomization, 3, 6, 12, 18, and 24 months. The answers range from "0 – minimal/does not interfere" to "10 – severe/completely interferes." Standard composite scores and change from baseline at each time point will be summarized with descriptive statistics by treatment group, stratification factors [prostate cancer risk (low/intermediate) and type of biopsy performed (mpMRI targeted/non-mpMRI targeted)], subgroups (age, race, and BMI at Screening) and overall. Composite scores for all licensed instruments will be calculated per the licensing agreements.

When there are missing data, if half or more questions within scale are answered then a score will be calculated for that scale. Otherwise the patient score for that scale will be missing. For single-item measures, a missing score will not be imputed.

BFI compliance and completion rates at each visit will be calculated using the following definitions:

- BFI compliance rate: will be defined as the proportion of patients who completed the PRO instrument among those who were expected to complete at each visit, excluding those missing by design (e.g. death, discontinuation of treatment, or no visit scheduled).

- BFI completion rate: defined as the proportion of patients who completed the PRO instrument at baseline and >=1 assessment subsequently among those who completed PRO baseline and are remaining in study at each follow up timepoint.

#### 7.4.2.4 SF-12

The Medical Outcomes Study 12-Item Short Form Survey (SF-12) is a questionnaire that measures overall health related quality of life using 12 questions, assessed at Randomization, 6, 12, 18, and 24 months. Summation of standardized questions' scores are used to calculate the PCS and MCS Composite Scores. Scores and change from baseline will be analyzed at each time point and overall in the same manner as the BFI scores. To distinguish clinically meaningful differences from statistically significant differences, the minimum clinically important difference (MCID) will be calculated using a distribution-based approach as 0.5 baseline score standard deviation pooled over treatment groups for each domain. Equivalence will be demonstrated when the entire 95% confidence interval for the adjusted mean difference or change is within the range from −MCID to + MCID.

Similar to BFI, SF-12 compliance and completion rates will be calculated at each visit.

#### 7.4.2.5 Expanded Prostate Cancer Index Composite (EPIC)

The EPIC Hormonal Assessment is a questionnaire used to measure quality of life issues in patients with prostate cancer. There are a total of 11 questions assessed at Randomization, 6, 12, 18 and 24 months related to hormonal function such as hot flashes, breast tenderness, depression, lack of energy, weight fluctuation, etc. The answers range from "more than once a day" to "rarely or never" and "no problem" to "big problem."

The EPIC Sexual Assessment is a questionnaire used to measure quality of life issues in patients with prostate cancer. There are a total of 13 questions assessed at Randomization, 6, 12, 18 and 24 months related to sexual function such as level of sexual desire, ability to have an erection, ability to reach orgasm, quality and frequency of erections, frequency of sexual intercourse, etc. The answers range from "very poor" to "very good," "never" to "daily," and "no problem" to "big problem."

The EPIC Urinary Assessment is a questionnaire used to measure quality of life issues in patients with prostate cancer. There are a total of 12 questions assessed at Randomization, 6, 12, 18 and 24 months related to urinary function such as leaking urine, blood in urine, pain or burning with urination, urinary control and frequency, etc. The answers range from "more than once a day" to "rarely or never" and "no problem" to "big problem."

Total composite and each domain score (hormonal, sexual, and urinary) and their corresponding change from baseline assessments will be analyzed by time point and overall in the same manner as the BFI scores.

If >20% of the items that comprise a domain summary score or subscale score are missing a response, the corresponding domain summary or subscale score can not be calculated).

To distinguish clinically meaningful differences from statistically significant differences, the minimum clinically important difference (MCID) will be calculated using a distribution-based approach as 0.5 baseline score standard deviation pooled over treatment groups for each domain score and the total composite score. Equivalence will be demonstrated when the

entire 95% confidence interval for the adjusted mean difference or change is within the range from −MCID to + MCID.

Similar to BFI, EPIC compliance and completion rates will be calculated at each visit for each of the EPIC assessments.

#### 7.4.2.6 Memorial Anxiety Scale for Prostate Cancer

The Memorial Anxiety Scale for Prostate Cancer (MAX-PC) is a questionnaire used to assess patients' feelings about prostate cancer and PSA tests. There are a total of 18 questions assessed at Randomization, 6, 12, 18 and 24 months related to understanding how patients cope with aspects of their treatment and medical tests frequently involved in their care; questions such as strong feelings about prostate cancer, scared of PSA tests, trouble sleeping due to thoughts of prostate cancer, unable to plan for the future due to prostate cancer, fear of cancer getting worse, etc. The answers range from "not at all" to "often" and "strongly disagree" to "strongly agree."

When there are missing data, if 66% or more questions within scale are answered then a score will be calculated for that scale. Otherwise the patient score for that scale will be missing. For single-item measures, a missing score will not be imputed.

Total composite scores and change from baseline will be analyzed by time point and overall in the same manner as the BFI scores. Composite scores for all licensed instruments will be calculated per the licensing agreements.

Data listings including individual scores, subscale scores and total scores will be provided by treatment group and visit for all patient reported outcomes.

To distinguish clinically meaningful differences from statistically significant differences, the minimum clinically important difference (MCID) will be calculated using a distribution-based approach as 0.5 baseline score standard deviation pooled over treatment groups for each domain score and the total composite score. Equivalence will be demonstrated when the entire 95% confidence interval for the adjusted mean difference or change is within the range from −MCID to + MCID.

Similar to BFI, MAX-PC compliance and completion rates will be calculated at each visit for each of the EPIC assessments.

#### 7.4.2.3 Cancer Positive Cores

Percent of cancer positive cores, assessed using the number of systemically-sampled prostate regions and any targeted regions with at least one positive core (see Section 6.4 for details), will be analyzed at Screening, 12, and 24 months.

Analyses of treatment group differences for the change from baseline composite score will be analyzed with a Mixed Model Repeated Measures (MMRM) model using subject and site as a random factors. For the variance- covariance matrix, compound symmetry (CS), autoregressive (AR1) and unstructured (UN) will be assessed and the best fit will be chosen based on Akaike Information Criteria (AIC) or AICC (correction for finite sample sizes). Degrees of freedom will be approximated using the Kenward-Roger method. Fixed effects will include treatment group, the stratification factors [prostate cancer risk (low/intermediate) and type of biopsy performed (mpMRI targeted/non- mpMRI targeted)], time, time-by-treatment interaction and baseline composite score. Estimates will include 95% confidence

intervals of least square means (LS Means) for each treatment group by nominal time point and overall. P-values will be adjusted using the bonferroni-holm method to adjust for multiplicity. Additionally, assessments of treatment group differences will be made at 3, 6, 12, and 24 months, as well as for the overall model.

### 7.4.3 [redacted] CCI

[redacted]

## 7.5 Analysis of Safety

The following summary tables and listings will be displayed for the SAF.

### 7.5.1 Adverse Events

All AEs will be collected and the severity of the AEs will be evaluated by the investigator based on Version 4.03 of the NCI-CTCAE criteria, updating to the latest version per sponsor decision. All AEs will be coded using the Version 23.0 of the Medical Dictionary for Regulatory Activities (MedDRA) to preferred term, high-level term and system organ class, up versioning every two years per sponsor decision.

Adverse events occurring before randomization will be recorded as medical history events. To maintain naming consistency with subjects on Active Surveillance (AS), Treatment-Emergent Adverse Events (TEAEs) for subjects on Enzalutamide will be reported as Adverse Events (AEs).

An overall summary table will be included that has the following information by treatment group and overall by analysis phase (Treatment, 1-Year Follow-Up and Continued Follow-Up):

- Number and percentage of subjects with AEs
- Number and percentage of subjects with causally drug-related AEs
- Number and percentage of subjects with serious AEs
- Number and percentage of subjects with serious drug-related AEs
- Number and percentage of subjects with AEs leading to permanent discontinuation of study drug,
- Number and percentage of subjects with drug-related AEs leading to permanent discontinuation of study drug
- Number of deaths.

Furthermore, the number of events and number (%) of subjects with AEs, drug-related AEs, serious AEs, drug-related serious AEs, AEs leading to permanent discontinuation of study drug, drug-related AEs leading to permanent discontinuation of study drug, and common AEs occurring in at least 3.5% of any treatment group will be summarized by MedDRA system organ class and preferred term by treatment group and overall. Additional summary tables will be provided for AEs by relationship to study treatment and by CTCAE maximum severity grade. For subjects with missing relationship, the most conservative (related) will be assumed for table summaries.

If a subject reports the same event multiple times, the event will only be displayed once in the summary tables at the highest grade and relationship to study drug.

Version 4.03 of the NCI-CTCAE criteria, updating to the latest version per sponsor decision, will be used to classify laboratory values by toxicity grade.

Listings of AEs, SAEs, Deaths and AEs leading to study drug discontinuation will be displayed by treatment group and site.

### 7.5.2 Clinical Laboratory Evaluation

Clinical laboratory assessments will be done at every scheduled visit, as well as at any unscheduled visits. Assessments of serum hormonal levels will be done at the

Randomization, 12 Month Visits, 24 month and at any unscheduled study visits. Summary tables will be presented for all scheduled visits. Unscheduled visits will be displayed in listings only. Values outside the normal range will be flagged.

Laboratory data in this study consist of hematology (WBC count, WBC differential, RBC count, RDW, HCT, HgB, MCV, MCH, MCHC, Platelet count, MPV), serum chemistry (Glucose, Calcium, Total protein, Albumin, Sodium, Potassium, CO2, Chloride, BUN, Creatinine, ALP, ALT, AST, Bilirubin), PSA levels and hormonal levels (Testosterone, DHT, Dihydroepiandrosterone, Androstenedione, Estradiol).

The results will be summarized by treatment group for actual values and change from baseline. Normal ranges will be applied to identify values that are outside the normal ranges. Shift analysis tables will be provided for each parameter to present shift from baseline to each visit for low, normal and high values.

Laboratory results will be graded using the Version 5.0 of the NCI-CTCAE criteria, updating to the latest version per sponsor decision. Shift tables will be produced and will report the baseline NCI-CTCAE grade vs. the worst grade recorded at any post-baseline visit.

#### 7.5.2.1 Liver Enzymes and Total Bilirubin

Detailed testing for liver enzymes, specifically ALT, AST, and Total Bilirubin, are done at every study visit starting with Randomization and up to month 24 and unscheduled.

Confirmed abnormalities will be characterized as moderate and severe where ULN:

Moderate: AST or ALT **[** >3 x ULN (in patients without liver metastases); >5 x ULN (in patients with liver metastases)] or (Total Bilirubin >2 x ULN).

Severe: AST or ALT >3 x ULN and Total Bilirubin >2 x ULN.

In addition, the subject will be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than 2 weeks (in the absence of liver metastases).
- ALT or AST > 3 × ULN and INR > 1.5 (If INR testing is applicable/evaluated).
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

### 7.5.3 Vital Signs

Vital signs [temperature (in Celsius), blood pressure (mmHg), pulse rate (beats/min), and respiratory rate (breaths/min)] will be summarized by treatment group at the Screening Visit and at all study visits for actual values and change from baseline. All data will be displayed in listings by treatment group and visit.

### 7.5.4 Electrocardiograms (ECGs)

12–Lead ECG will be performed at the Screening visit only and summarized with the baseline characteristics summary by treatment group.

### 7.5.5 Transrectal Ultrasound-guided Prostate Biopsy and Lesion Details

Results from the Transrectal ultrasound-guided prostate biopsy at Screening, 12 and 24 months will be summarized in tables and displayed in data listings. Descriptive statistics will

be included for continuous endpoints and frequency and percentage for categorical endpoints. Lesion details will be summarized in a table by visit and treatment group and displayed in data listings.

### 7.5.6 Physical Examinations

General physical examination will be performed at Screening and any abnormal finding will be reported in the medical history form should the finding occur prior to randomization, or on the AE form post-randomization. Therefore, no physical examination data will be displayed.

A breast exam will be performed at the Screening Visit and at all study visits except the Randomization Visit. Results of the exam will be summarized in a table by treatment group and included in a subject listing. Any other abnormal findings/conditions identified during the breast exam are reported in the medical history form or AE form.

Prior digital rectal examination and current rectal examination results will be summarized by treatment group at the Screening, 6 Month, 12 Month, 18 Month and 24 Month Visits, as well as at the biannual (every 6 months) visits following the 24 Month Visit. Exam results will be also be displayed in a subject listing.

## 7.6 Analysis of PK

Not Applicable

## 7.7 Analysis of PD

Not Applicable.

## 7.8 Subgroups of Interest

Subgroup analyses of time to progression will be performed to evaluate the treatment effect based on the following subgroups separately: age (<65, 65 to <75, and >=75), race (white, black or African American, and the combined categories of Asian, American Indian or Alaska native, Pacific islander), and BMI (<25; 25-30; and >30).

## 7.9 Interim Analysis (and Early Discontinuation of the Clinical Study)

Not Applicable

## 7.10 Handling of Missing Data, Outliers, Visit Windows, and Other Information

### 7.10.1 Missing Data

As a general principle, no imputation of missing data will be done. Exceptions are the start and stop dates and relationship of AEs and CMs and visit windows.

All analysis will be based on available data to summarize safety and efficacy results. However, a conservative approach to partial dates and missing adverse event relationships will be as follows:

- For survival analyses, if a subject's death month and year are provided but the day is missing, the day will be set to the first day of the month, unless other qualifying study data support survival until a later date in the same month.
- For subjects in the enzalutamide arm, adverse events with partial dates with the same month and year as the first dose date of study drug will be considered as treatment-emergent adverse events.
- For subjects in the enzalutamide arm, if an adverse event's relationship is missing, it will be assumed to be related.
- For subjects in the enzalutamide arm, if the AE or CM start day is missing, then impute the 1st of the month unless month and year are the same as the month and year of first dose of study drug, then impute AE/CM start date with the first dose date. If the start month and day are both missing, then impute 01JAN unless the year is the same as first dose date, then impute AE/CM start date with the first dose date. If the entire start date is missing, then no imputation will be performed, but the AE will be considered treatment-emergent.
- For subjects on active surveillance, if the AE or CM start day is missing, then impute the 1st of the month unless month and year are the same as the month and year of randomization, then impute AE/CM start date with the randomization date. If the start month and day are both missing, then impute 01JAN unless the year is the same as randomization date, then impute AE/CM start date with the randomization date. If the entire start date is missing, then no imputation will be performed, but AE will be considered to have occurred on or after randomization date.
- For subjects in the enzalutamide arm, if the adverse event or concomitant medication end day is missing, then impute the last day of the month unless month and year are the same as month/year of last dose of study drug, then impute last dose date. If the end month and day are both missing, then impute 31DEC unless year is the same as first dose date, then impute last dose date. If the entire end date is missing, then no imputation will be performed and the event will be considered "ongoing."
- For subjects on active surveillance, if the adverse event or concomitant medication end day is missing, then impute the last day of the month unless month and year are the same as month/year of last day of 1 year of active surveillance, then impute last date on active surveillance. If the end month and day are both missing, then impute 31DEC unless year is the same as randomization date, then impute last date on active surveillance. If the entire end date is missing, then no imputation will be performed and the event will be considered "ongoing."

All AE and concomitant medication imputation of missing dates and relationship will be

considered for tabular summaries but not for data listings. Data listings will display missing values. Subjects who do not receive the study drug to which they have been randomized will be analyzed as treated.

### 7.10.2 Outliers

All values will be included in the analyses.

### 7.10.3 Visit Windows

For reporting by nominal time point, assessments will be imputed with the following windowing conventions:

| Nominal Visit | Target Study Day (per Section V of the Protocol) | Study Day Window (inclusive) |
|---|---|---|
| 3 Month | 85 | 43 to 130 |
| 6 Month | 176 | 131 to 221 |
| 9 Month | 267 | 222 to 312 |
| 12 Month | 358 | 322 to 406 |
| 15 Month | 455 | 407 to 500 |
| 18 Month | 545 | 501 to 590 |
| 21 Month | 635 | 591 to 682 |
| 24 Month | 730 | 683 to 754 |

For nominal time points with a nominal visit corresponding, this value will be used. If no nominal assessment exists, but an unscheduled assessment is windowed into the time point, this windowed assessment will be used. If more than one unscheduled assessment exists in the window (and there is no nominal visit assessment), the latest value will be used.

### 7.10.4 Site Pooling

Data will be pooled from sites for these analyses. The justification for pooling is made on a clinical basis (Meinert, 1986). The basis for pooling comes from three critical factors: 1) The study sites must implement one common protocol. 2) The sponsor must provide very close monitoring of study site compliance. 3) The study sites must use common data collection procedures.

# 8 SAP DEPARTURES FROM THE PROTOCOL

- [redacted] CCI [redacted]
- Primary and secondary analysis will be done separately for therapeutic and pathological progression, in addition to overall.
- FAS and SAF would be different in the case of subjects randomized to enzalutamide treatment group end up discontinuing before taking a single dose of the study drug
- It is unlikely but possible to have dose increases. Such a possibility has been accounted for in the relevant table and listing.
- "Age" will be an additional fixed effect used in the statistical models.
- "Site" will be an additional random effect used in the statistical models.
- [redacted] CCI [redacted]
- ENACT study is conducted in patients with localized disease who are candidate for Active Surveillance, the use of questionnaire such as BFI, SF-12, MAX-PC and EPIC have not been validated in this patient population, as a result analysis of PROs will be limited to descriptive statistics. The details of descriptive analyses can be found in respective PRO sections.
- All analyses will be performed separately by stratification factors [prostate cancer risk (low/intermediate) and type of biopsy performed (mpMRI targeted/non mpMRI targeted)].

# 9 DOCUMENT REVISION HISTORY

| Version | Date | Changes | Comment/rationale for change |
|---|---|---|---|
| 1.0 | 21-SEP-2016 | Minor updates to verbiage | Final v1.0 based on client review of second draft |
| 2.0 | 16-OCT-2020 | Updates throughout document, including revised shells, additions to the exploratory analyses andrenumbered TFLs. | Final v2.0 based on client review |

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# 11 APPENDICES

## 11.1 Appendix 1: Key Contributors and Approvers

# List of Key Contributors and Approvers

### Key Contributors

The following contributed to or reviewed this Statistical Analysis Plan as relevant to their indicated discipline or role.

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| | |
|---|---|
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