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Statistical Analysis Plan

Title of trial: A Multi-Center, Randomized, Assessor-Blind, Controlled Trial Comparing the Occurrence of Major Adverse Cardiovascular Events (MACEs) in Patients with Prostate Cancer and Cardiovascular Disease Receiving Degarelix (GnRH Receptor Antagonist) or Leuprolide (GnRH Receptor Agonist)
NCT number: NCT02663908
Sponsor trial code: 000108
Date: 24 Feb 2021

STATISTICAL ANALYSIS PLAN

A Multi-Center, Randomized, Assessor-Blind, Controlled Trial Comparing the Occurrence of Major Adverse Cardiovascular Events (MACEs) in Patients with Prostate Cancer and Cardiovascular Disease Receiving Degarelix (GnRH antagonist) or Leuprolide (LHRH agonist)

000108

IND Number: 051222

Investigational Medicinal Product : Degarelix powder and solvent for solution for injection

Leuprolide acetate 22.5 mg 3 month depot

Indication: Prostate cancer

Phase: 3b

Authors: [redacted]

Date of issue: 24 February 2021

Version: 7.0

Change log

Version No.	Effective Date	Reason for the Change / Revision	Supersedes
1	Dec 16 – 2015	Original SAP	Not Applicable
2	Dec 18 – 2015	Format Change only. No content was changed.	Version 1.0
3		The list of major protocol deviations in Section 5 was updated to reflect the changes to the clinical trial protocol introduced with clinical trial protocol amendment #01.	Version 2.0
4	Mar 28 - 2017	To update the SAP in order to relect the revised eligibility criteria for the trial based on recommendations from the Steering Committee and changes made to the trial protocol in agreement with the US Food and Drug Administration (FDA) following review of the Clinical Trial Protocol Amendment number 01, dated 21 September 2016.	Version 3.0
5	Nov-18-2019	The list of key secondary endpoints has been revised, and sensitivity endpoint "Time from randomization to the first confirmed (adjudicated) occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke" has been added to the list, and the testing strategy has been changed from Holm's to a fixed. Also, PP analyses have been reduced to primary and exploratory endpoints.	Version 4.0

6	Sep 30 - 2020	Due to the trial being terminated early, the SAP was updated. The following changes has been made to the SAP: - Due to site errors in randomizations, the FAS will be used instead of ITT in order to present "correct" denominator in tables. - Planned interim analyses have been cancelled. - Various changes to analyses no longer affected by the expected interim. - Sensitivity analyses of the primary endpoint including PP analyses have been cancelled. - Some analyses have been reduced (not removed) as deemed unnecessarily extensive, others have been slightly altered. - Analyses regarding markedly abnormal laboratory values have been cancelled as deem unnecessary by pharmacovigilance.	Version 5.0
7	Feb-24-2021	Sensitivity analyses added to primary analysis. Slight rewording of some endpoints. Endpoint "Total number of emergency room (ER) visit events over the duration of the trial" changed to "Total number of CV-related emergency room (ER) visit events over the duration of the trial". Treatment switch definition updated according to data collected. Important deviations to be summarized. General rewordings and clarifications added.	

Signed Agreement on Statistical Analysis Plan

Author: [redacted] Statistician, Global Biometrics

The statistical analysis plan was reviewed by,

[redacted] Urology, Global Clinical Development, Ferring Pharmaceuticals A/S

[redacted] Urology, Global Clinical Development, Ferring Pharmaceuticals A/S

[redacted] Statistician, Global Biometrics, Ferring Pharmaceuticals A/S

[redacted] Statistical Programmer, Global Biometrics, Ferring Pharmaceuticals A/S

[redacted] Clinical Trial Manager, Global Clinical Operations, Ferring Pharmaceuticals A/S

[redacted] Pharmacovigilance physician, Global Pharmacovigilance, Ferring Pharmaceuticals A/S

[redacted] Medical Writer, Global Medical Writing, Ferring Pharmaceuticals A/S

The statistical analysis plan was reviewed and approved (signed electronically) by,

[redacted] Global Biometrics, Ferring Pharmaceuticals A/S

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 Introduction

This document describes the planned statistical analyses for Trial 000108.

1.1 Abbreviations

ADT	Androgen Deprivation Therapy
AIC	Akaike Information Criterion
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
CABG	Coronary Artery by-pass Grafting
CAQ	Cardiac Anxiety Questionnaire
CDF	Cumulative Distribution Function
CEC	Clinical Events Classification
CI	Confidence Interval
CV	Cardiovascular
CVD	Cardiovascular Disease
DASI	Duke Activity Status Index
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EQ-5D-5L	EuroQol Group 5 Dimensions Questionnaire
ER	Emergency Room
FAS	Full Analysis Set
FPR	False Positive Rate
GnRH	Gonadotropin-Releasing Hormone
HbA_{1c}	Hemoglobin A_{1c}
HRQL	Health-Related Quality of Life
[redacted]	[redacted]
IMP	Investigational Medicinal Product
IPCW	Inverse Probability of Censoring Weights
IPSS	International Prostate Symptom Score
ITT	Intention-to-Treat
KMMI	Kaplan-Meier Multiple Imputation
LHRH	Luteinizing Hormone Releasing Hormone
LUTS	Lower Urinary Tract Symptoms
MACE	Major Adverse Cardiovascular Event
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
[redacted]	[redacted]
PCA	Prostate cancer
PCI	Percutaneous Coronary Intervention
PFS	Progression-Free Survival
PP	Per Protocol
PRO	Patient Reported Outcome
PSA	Prostate-specific Antigen
PT	Preferred Term
QALY	Quality Adjusted Life Year

ROC	Receiver Operating Characteristics
SOC	System Organ Class
TPR	True Positive Rate
WHO	World Health Organization
WLW	Wei – Lin – Weissfeld

2 Trial Objectives and Endpoints

2.1 Objectives

2.1.1 Primary Objective

- The primary objective is to assess the effect of a GnRH receptor antagonist (degarelix) on the risk of occurrence of MACEs (a composite of death due to any cause, non-fatal myocardial infarction or non-fatal stroke) as compared to a GnRH receptor agonist (leuprolide) in patients with prostate cancer and concomitant CVD

2.1.2 Secondary Objectives

CV and Death Related Objectives

- To assess the rate of specific MACEs (individual components of the composite MACE endpoint), i.e. myocardial infarction (fatal, non-fatal), stroke (fatal, non-fatal), in patients randomized to degarelix versus leuprolide
- To assess the rate of unstable angina requiring hospitalization (fatal, non-fatal), in patients randomized to degarelix versus leuprolide
- To assess the risk of death due to any cause in patients randomized to degarelix versus leuprolide
- To assess the rate of cardiovascular (CV)-related death in patients randomized to degarelix versus leuprolide

Prostate Cancer-Related Objectives

- To monitor testosterone levels at Day 28, 168 and 336 in the degarelix and leuprolide treatment groups
- To evaluate the progression-free survival (PFS) failure rates (defined as either death, radiographic disease progression[a], introduction of additional therapy related to prostate cancer[b] or prostate-specific antigen [PSA] failure[c], whichever is first) in the degarelix and leuprolide treatment groups
  a. One or more new metastatic skeletal lesions observed on bone scan; one or more new metastatic extra-skeletal lesions at least 1.5 cm in greatest dimension visible on computed tomography or magnetic resonance imaging (MRI) scan as confirmed by the Investigator.
  b. Additional therapy includes radiation, anti-androgens (except for initial symptomatic flare protection) and second-line treatment.
  c. PSA failure is defined as an increase in serum PSA of 50%, and at least 5 ng/mL, compared to nadir, measured on two consecutive occasions at least 2 weeks apart.
- To compare the effects of degarelix with leuprolide with regards to local urinary tract and prostate cancer-related symptoms with the International Prostate Symptom Score (IPSS) questionnaire

Health Economics and Patient Reported Outcome (PRO) Objectives

- To compare the effects of degarelix with leuprolide with regards to healthcare resource use

- To compare the effects of degarelix with leuprolide with regards to health status through the EuroQol Group 5 Dimensions Questionnaire (EQ-5D-5L)
- To compare the effects of degarelix with leuprolide with regards to functional capacity and Quality of Life (QoL) through the Duke Activity Status Index (DASI)
- To compare the effects of degarelix with leuprolide with regards to heart-focused anxiety through the Cardiac Anxiety Questionnaire (CAQ)

Safety Objective

- To evaluate and compare the overall safety and tolerability of degarelix with leuprolide

2.1.3 Exploratory Objectives

- To compare the effects of degarelix with leuprolide with regards to a second confirmed (adjudicated) occurrence of the composite MACE endpoint, in the subgroup of patients that survived the first CV event

- [redacted]

- [redacted]

2.2 Endpoints

2.2.1 Primary Endpoint

- Time from randomization to the first confirmed (adjudicated) occurrence of the composite MACE endpoint

2.2.2 Secondary Endpoints

Key Secondary Endpoints

- Time from randomization to the first confirmed (adjudicated) occurrence of CV-related death, non-fatal myocardial infarction or non-fatal stroke
- Time from randomization to confirmed (adjudicated) CV-related death
- Time from randomization to the first confirmed (adjudicated) myocardial infarction

Other CV and Death-Related Endpoints

- Time from randomization to the first confirmed (adjudicated) stroke
- Time from randomization to the first confirmed (adjudicated) unstable angina requiring hospitalization
- Time from randomization to death due to any cause

Prostate Cancer-related Endpoints

- Testosterone levels at Days 28, 168 and 336 in the degarelix and leuprolide treatment groups
- Time from randomization to failure in PFS
- Changes from baseline in IPSS Total and Qol scores

Health Economics and Patient-Reported Outcomes Endpoints

- Total number of CV-related hospitalization events over the duration of the trial
- Total number of coronary artery by-pass grafting (CABG) or percutaneous coronary intervention (PCI) procedures over the duration of the trial
- Total number of CV-related emergency room (ER) visit events over the duration of the trial
- Change in utility, based on EQ-5D-5L
- Changes from baseline in DASI Global score
- Changes from baseline in CAQ Global score and score per domain

Safety Endpoints

- Incidence and intensity of adverse events
- Changes in vital signs

2.2.3 Exploratory Endpoints

- Time from first adjudicated non-fatal MACE to a second confirmed (adjudicated) occurrence of the composite MACE endpoint in the subgroup of patients that survived the first CV event

[redacted]

[redacted]

3 Trial design

The following section details the original trial design. However, the trial was terminated due to feasibility problems, with only 545 patients randomized and 14 of those with positively adjudicated events. Hence, many of these sections no longer apply.

3.1 General Design Considerations

This is a multi-center, randomized, assessor-blind, controlled trial to compare MACEs in patients with prostate cancer and concurrent CVD receiving either monthly treatment with degarelix or leuprolide 3-month depot for 1 year. Patients will be screened within 8 to 21 days prior to randomization for compliance with the inclusion and exclusion criteria. A trial design diagram is provided in Figure 1.

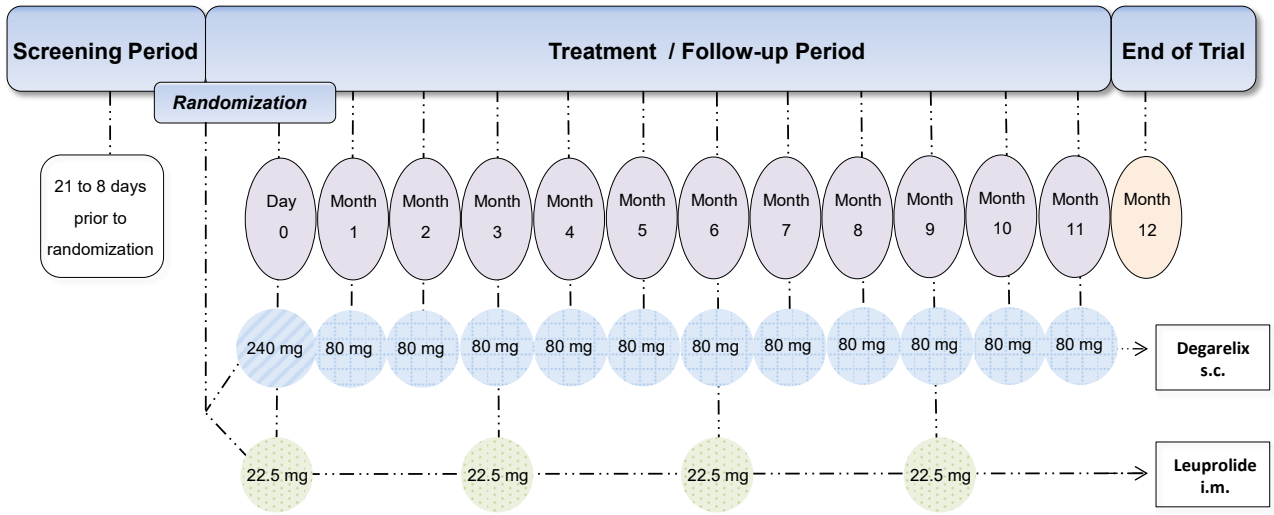

Figure 1 Trial Design Diagram

Patients will be randomized to one of the two treatments in a 1:1 ratio stratified by age group (<75 and ≥75 years of age) and region (North America, other). After randomization, the management of prostate cancer is intended to reflect standard-of-care. Monitoring for possible MACEs will occur throughout the trial applying a specific Clinical Events Classification (CEC) process ensuring blinding of the event assessors.

3.2 Determination of Sample Size

The primary objective is to assess the effect of degarelix on the risk of MACEs (a composite of death due to any cause, non-fatal myocardial infarction or non-fatal stroke) occurring during a 1-year period as compared to treatment with leuprolide in patients with prostate cancer and concomitant CVD.

The observed one-year event rates for primary MACE endpoint are 5.3% and 12.1% for degarelix and LHRH agonist, respectively, in the global patient population with prior CVD were derived from a post-hoc analysis of degarelix safety data. This would correspond to an unadjusted treatment-

related hazard ratio of 0.42. (In comparison, the adjusted hazard ratio is 0.39 (95% confidence interval [CI] = [0.21; 0.71]).) Furthermore, based upon the re-assessment of the potential CV events captured in the degarelix safety data by an independent cardiologist, the one-year event probability for CV event or death due to any cause are 4.8% and 9.3% for degarelix and leuprolide respectively. This corresponds to an unadjusted hazard ratio of 0.50 (in comparison, the adjusted hazard ratio is 0.48 (95% confidence interval is [0.23,0.87]). Accounting for the uncertainty in the post-hoc analysis of the global pooled data and the re-assessment of the potential CV events by a single independent cardiologist, the one-year event rates for sample size calculations are set to 5.1% and 10.2% for degarelix and leuprolide, respectively. This corresponds to a hypothesized hazard ratio of 0.49.

3.2.1 Fixed Trial Design

Given the alternative hypothesis, a power of 80% and a signficiance level of 5%, the expected number of events required at the final analysis is 61. The sample size required for achieving this number of events assumes that all patients are followed-up for primary outcome (MACEs) for 12 months (28 days each) after start of treatment and an annual drop-out rate of 5%. Assuming these characteristics a total sample size of 811 patients is required.

3.2.2 Adjustments for Futility Analyses

One interim analysis is planned after 50% of the confirmed, adjudicated MACE endpoints have been collected. One of the objectives of the interim analysis is to test whether there is any reason to stop early for futility. The futility bound expressed in terms of the hazard ratio is 0.78. That is, if the observed hazard ratio is >0.78 the Data and Safety Monitoring Board (DSMB) may suggest to stop the trial due to futility. The futility bounds are non-binding. Due to the possibility to stop early for futility the power is deflated (risk of stopping a successful trial is inflated), and to reinstall the power at 80% the number of required events is inflated to 66 and the total number of patients to 876.

The trial will not be stopped early due to an overwhelming treatment benefit, but in order to implement the trial design, an alpha-spending function will be used with nearly zero spending of alpha at the interim analysis, $\alpha < 0.0001$ (e.g. trial will not be stopped early for efficacy).

3.2.3 Adjustments for Sample Size Re-Estimation

The conditional power for different sample size increases will be evaluated at the interims using SAS. In case of a sample size increase, the final test statistic is adjusted by using the normal inverse method in order to protect the two-sided Type I error rate at 5%.

The sample size calculations are performed with ADDPLAN™ 6, licensed by ADDPLAN, Inc., an Aptiv Solutions company and presented in Table 1.

Table 1 Sample Size Calculations (Number of Events Rounded Upwards)

Information Rate	Stop for futility/No evidence reject H_0			Successful trial (Reject H_0)	α spent	Power	Events
	Test Statistic	Hazard Ratio	Conditional Power	Test Statistic			
50%	≤ 0.7	≥ 0.78	≤ 8.5%	-	< 0.0001	-	33
100%	≤ 1.96	≥ 0.61	-	≥ 1.96	0.025	80%	66

- Assuming constant hazards, $\lambda_{degarelix} = 0.0523/year$ $\lambda_{leuprolide} = 0.1076/year$
- 5% drop out rate in each arm
- 1:1 randomization ratio

When d, the number of events, has been observed, the approximate relationship between the standardized test statistic, Z, and the hazard ratio (HR) as given in (Jennison and Turnbull, 2000) is,

$$\boldsymbol{Z \approx log(HR^{-1})\sqrt{d/4}}$$

For reasons of interpretation, both Z and the hazard ratio are reported in design tables.

4 Patient Disposition

All patients screened and randomized will be accounted for. All post-randomization discontinuations will be summarized by time of, and reason for, discontinuation. The number of patients screened and not randomized will be presented with the reason(s) for screen failure.

Special attention should be paid to those patients who discontinue treatment with investigational medicinal product (IMP) and start an alternative treatment during the trial, including the dates corresponding to going off the randomized drug, i.e. the date of the last injection and the start of a new treatment, i.e. the date the new treatment was initiated.

In addition, the breakdown of the overall disposition of patients by age group (<75 years of age, ≥75 years of age) and region following the design (stratification) of the trial will be provided. Also, the number of patients screened and randomized, overall and by age group (<75 years of age, ≥75 years of age) and region will be provided.

1- Kaplan–Meier (1-KM) plots of the time to early discontinuation, as well as the time to treatment discontinuation or initiation of prohibited therapies related to hormonal therapy, will be displayed per treatment arm. In addition, time to early discontinuation by reason for discontinuation and treatment arm will be presented by cumulative incidence function curves. Differences in discontinuation rates and treatment discontinuation or initiation of prohibited therapies related to hormonal therapy rates between treatment groups will be tested using the Log Rank test (α=0.05, two-sided).

5 Protocol Deviations

As no PP analyses are planned, there will be no classification of 'minor'/'major' events, reflecting potential impact on efficacy endpoints due to protocol violations.

In order to reflect general (i.e. not specifically related to impact on efficacy) protocol adherence important deviations will be summarized by treatment group and category, and listed by subject for the Full Analysis Set.

6 Analysis Sets

6.1 Intention-To-Treat Analysis Set

The Intention-to-Treat (ITT) analysis set consists of all randomized patients, and will be analysed based on the planned (randomized) treatment.

6.2 Full Analysis Set

The Full Analysis Set (FAS) consists of all randomized and treated patients (who received at least one dose of IMP), and will be analysed based on the planned (randomized) treatment.

6.3 Safety Analysis Set

The Safety analysis set consists of all treated patients (who received at least one dose of IMP), and will be analysed based on the actual treatment received.

7 Trial Population

All tables will be presented for the FAS.

7.1 Demographics and Other Baseline Characteristics

Categorical data will be summarized using numbers and percentages. The percentages are based on the total number of patients with a corresponding assessment. Continuous data will be presented, for example, using the number of patients (N), mean and standard deviation, median, minimum and maximum. All baseline characteristics will be listed.

7.1.1 Demographics

[redacted]

7.1.2 Vital Signs at Baseline

[redacted]

7.1.3 History and Stage of Prostate Cancer

A summary table of history and stage of PCA will be presented, containing the following information:

- Gleason score (as defined below)
- Stage of prostate cancer (TNM classifications, as defined below)
- ECOG performance score

The following pathological stages will be recorded and summarized by treatment group, age (<75 years and ≥75 years) and region:

The Gleason score is calculated as the sum of the Gleason grade of the primary and secondary patterns. The following categories will be presented:

- 2-4
- 5-6
- 7-10

The stage of prostate cancer, based on the TNM classification, includes the following categories:

- Localised: T½ & (NX or N0) & M0,
- Locally Advanced: [T¾ & (NX or N0) & M0], or [N1 & M0],
- Metastatic: M1

- Not classifiable: Results from T, N, and M categories that could not be resolved to Localised, Locally Advanced, or Metastatic

[redacted]

7.1.5 Laboratory Efficacy / Pharmacodynamic Parameters at Baseline

Baseline variables will be summarized by treatment, age (<75 years and ≥75 years) and region.

[redacted]

7.4 Physical Examination

Patients with abnormalities at any screening, baseline, or post-baseline visit will be listed with all physical examination evaluations.

8 Exposure and Treatment Compliance

All tables will be presented for the FAS.

8.1 Extent of Exposure

The cumulated dose administered to each patient will be determined and summarized descriptively. For patients discontinuing the trial early, are lost to follow-up or initiate treatment with an ADT other than Degarelix or Leuprolide, their cumulated dose will be calculated up until the time of early discontinuation/lost to follow-up/treatment iniation.

8.2 Treatment Compliance

Treatment compliance will be presented from data listings. Patients not receiving the scheduled dose will be listed by center, sorted by treatment group and patient number.

9 Efficacy

The following sections detail the planned analyses in the protocol. Any changes to the planned analysis in the protocol are described in Section 12.

9.1 General Considerations

The analysis of efficacy will be performed for the FAS (unless otherwise specified). For the purpose of this CV outcome study, patients prematurely discontinuing from treatment will be followed-up for the occurrence of MACE events based on monthly telephone interviews. Unless otherwise stated, time to event endpoints will be censored at the time of treatment discontinuation, initiation of prohibited therapies related to hormonal therapy, lost to follow-up/withdrawal from the study or day 336, whichever occurs first. Initiation of prohibited therapy related to hormonal therapy includes the following:

- Surgical castration or other hormonal manipulation in addition to the IMPs
- Anti-androgens for combined androgen blockade (anti-androgen use for initial flare protection is allowed for a maximum period of up to 28 days after randomization)
- Estrogens
- Megestrol acetate
- Ketoconazole
- Abiraterone
- Enzalutamide
- Any additional hormonal therapy initiated as a combination therapy with the IMP

The associated ATC and MedDRA codes for the above prohibited therapies are provided in Table 11 and Table 12. Hypothesis tests will be two-sided at a significance level of 5% and missing data will not be imputed. 95% confidence limits and the associated p-values will be presented for estimates of the treatment effect comparing degarelix to leuprolide for all regression analyses.

For the purposes of this trial, [redacted]

[redacted]

[redacted]

[redacted]

9.2 Primary Endpoint

9.2.1 Primary Endpoint Analysis

The primary endpoint, the time from randomization to the first adjudicated occurrence of the composite MACE endpoint in the two treatment groups, will be analyzed using the Kaplan-Meier estimator of the survival function and the log-rank test, stratified for age (<75 and ≥75 years of age) and region and based on the FAS.

Pseudo SAS code for Kaplan-Meier/log-rank test:

```
PROC LIFETEST DATA=<DATA> PLOTS=SURVIVAL();
    TIME AVAL*CNSR(1);
   STRATA <STRAT1 STRAT2> /GROUP=ARMN TEST=LOGRANK;
RUN;
```

The hazard ratio, comparing the hazard rate of the distribution of the time from randomization to the MACE composite endpoint between the degarelix and leuprolide arms, will be estimated based on the stratified Cox regression model, stratified by age-group and region and including treatment as a factor. The variance estimate of the log hazard ratio will be obtained from the inverse of the observed information matrix for the partial likelihood. An approximate 95% CI for the hazard ratio will be calculated by exponentiation of the 95% CI for the log hazard ratio. Although, the score test for this stratified Cox Regression model is equivalent to the stratified log-rank test, (Kalbfleisch and Prentice, 2002), the (Wald based) 95% CI may not be fully consistent with the stratfied log-rank test. The latter, however, defines the success of the trial. More precisely, the trial will be declared positive if a statistically significant (at two-sided 5% significance level) reduction in the hazard rate of the time from randomization to the composite MACE endpoint is demonstrated in the FAS based on the stratified log-rank test, for patients randomized to degarelix compared to leuprolide.

TLF Figure: Primary Endpoint: Time to First Adjudicated MACE – FAS

9.2.2 Sensitivity Analyses

9.2.2.1 Sensitivity Analysis: Time from randomization to the first confirmed (adjudicated) occurrence of non-fatal myocardial infarction, non-fatal stroke, non-fatal unstable angina requiring hospitalization, or all-cause death

Time from randomization to the first confirmed (adjudicated) occurrence of non-fatal myocardial infarction, non-fatal stroke, non-fatal unstable angina requiring hospitalization, or all-cause death is defined similarly as the primary endpoint with the addition of cardiovascular events unstable angina requiring hospitalization. Also, the endpoint will be analyzed as for the primary endpoint.

9.2.2.2 Sensitivity Analysis: Time to first confirmed occurrence of a MACE related adverse event (MI SMQ (broad); Central nervous system hemorrhages and cerebrovascular conditions SMQ (broad); all-cause death)

Time to first confirmed occurrence of a MACE related adverse event is defined as for the primary endpoint with events being; any adverse event within the broad SMQ term 'myocardial infarction', any adverse event within broad SMQ term 'Central nervous system hemorrhages and cerebrovascular conditions' or all-cause death. Also, the endpoint will be analyzed as for the primary endpoint.

9.2.2.3 Sensitivity Analysis: Total occurrence of (adjudicated) myocardial infarction, stroke, and all-cause death

Total occurrence of myocardial infarction (MI), stroke and all-cause death is defined as the total number of events (MI, stroke or death) occurring over the duration of the trial.

The endpoint will be compared between treatment groups using a negative binomial model. The estimated treatment difference with a 95% confidence interval will be presented.

9.2.2.4 Sensitivity Analysis pertaining to treatment discontinuation or initiation of prohibited therapies related to hormonal therapy

For the purposes of this sensitivity analysis, patients will NOT be censored at the time of treatment discontinuation or initiation of prohibited therapies related to hormonal therapy. Rather, information pertaining to all observed occurrences of the first adjudicated MACE event in patients randomized in the study will be used. Patients will be censored at lost to follow-up/withdrawal from study or day 336, whichever occurs first.

9.3 Secondary Endpoints

If the primary analysis is significant at the two-sided Type I error-level of 5% the testing of the secondary endpoints will proceed as described below.

Key Secondary Analyses

The following analyses are included in the family of key secondary analyses:

- Time from randomization to the first confirmed (adjudicated) occurrence of CV-related death, non-fatal myocardial infarction or non-fatal stroke
- Time from randomization to confirmed (adjudicated) CV-related death
- Time from randomization to the first confirmed (adjudicated) myocardial infarction

The key secondary endpoints will be controlled for multiplicity (to ensure the family wise error rate is protected at a two-sided 5% Type I error-level) using a fixed-sequence testing method. The order of the testing sequence is as follows:

1. Time from randomization to the first confirmed (adjudicated) occurrence of CV-related death, non-fatal myocardial infarction or non-fatal stroke
2. Time from randomization to confirmed (adjudicated) CV-related death
3. Time from randomization to the first confirmed (adjudicated) myocardial infarction

The remaining secondary endpoints will be analyzed without controlling for multiplicity.

Other Secondary Analyses

- Time from randomization to the first confirmed (adjudicated) stroke
- Time from randomization to first confirmed (adjudicated) unstable angina requiring hospitalization
- Time from randomization to death due to any cause
- Time from randomization to failure in PFS
- Testosterone levels at Days 28, 168 and 336 in the degarelix and leuprolide treatment groups
- Total number of CV-related hospitalizations over the duration of the trial
- Total number of CABG or PCI procedures over the duration of the trial
- Total number of CV-related ER visit events over the duration of the trial
- Changes from baseline in Health-Related Quality of Life (HRQL) as measured by EQ-5D-5L, during the course of treatment period
- The difference in QALY during one year of treatment with degarelix compared to leuprolide
- The change from baseline in the mean DASI and CAQ score during one year of treatment with degarelix compared to leuprolide
- The change from baseline in the mean total and QoL IPSS score during oneyear of treatment with degarelix compared to leuprolide

9.3.1 Time from randomization to the first confirmed (adjudicated) occurrence of cardiovascular-related death, non-fatal myocardial infarction or non-fatal stroke

This endpoint is identical to the primary endpoint, only counting CV-related deaths, and not all cause deaths as failures. The time measured in days, from randomization to first confirmed (adjudicated) occurrence of CV-related death, non-fatal myocardial infarction or non-fatal stroke,

will be analyzed using the Kaplan-Meier estimator of the survival function and the log-rank test of the null hypothesis of equal hazard functions, stratified by age group and region. The p-value of the two-sided log-rank test with significance level of 5% will be presented along with plots of the estimated survival functions for the two treatment groups, stratified by age group and region. The treatment effect of degarelix will be further examined by fitting a stratified Cox regression model. The model will include treatment as a factor, be adjusted for the baseline CV risk factors as appropriate and stratified by age-group and region. The 95% confidence limits and associated p-value for the hazard ratio comparing treatment with degarelix to leuprolide will be presented.

TLF Table: Secondary Endpoint: CV Death + MI + Stroke – FAS

TLF Figure: Secondary Endpoint: CV Death + MI + Stroke – FAS

9.3.2 Time From Randomization to the first (adjudicated) occurrence of the individual components of the MACE composite endpoint

Time from randomization to the first adjudicated occurrence of the individual components of the MACE composite endpoint is defined as the number of days from randomization to the first adjudicated myocardial infarction / stroke. The occurrence of the components of the MACE composite endpoint will be adjudicated by the external independent CEC Committee. In order to correctly assess the treatment effect associated with degarelix with respect to the time to individual components of the MACE composite endpoint, it is necessary to account for the competing risk, death due to other causes. The above components of the MACE composite endpoint will be analyzed separately. The log-rank test stratified by age-group and region will be used to examine the null hypothesis of equal cumulative cause specific hazard functions. The p-value of the two-sided log rank test with significance level of 5% will be presented along with the plots of the estimated cumulative cause specific hazard functions for both treatments obtained from the Nelson-Aalen estimator, stratified by age group and region.

TLF Table: Secondary Endpoint: Time to First Adjudicated Myocardial Infarction – FAS

TLF Figure: Cumulative Cause Specific Hazard Function for Time to First Adjudicated Myocardial Infarction – FAS

TLF Table: Secondary Endpoint: Time to First Adjudicated Stroke – FAS

TLF Figure: Cumulative Cause Specific Hazard Function for Time to First Adjudicated Stroke – FAS

9.3.3 Time from randomization to the first confirmed (adjudicated) unstable angina requiring hospitalization

Time from randomization to the first adjudicated occurrence of unstable angina requiring hospitalization will be analyzed in the same manner as the individual components of the MACE primary endpoint, specified in Section 9.3.2.

TLF Table: Secondary Endpoint: Time to First Adjudicated Unstable Angina Requiring Hospitalization – FAS

TLF Figure: Cumulative Cause Specific Hazard Function for Time to First Adjudicated Unstable Angina Requiring Hospitalization – FAS

9.3.4 Time From Randomization to Death Due to Any Cause

Time from randomization to death due to any cause (overall survival, OS), is defined as the number of days from randomization to death. The time measured in days, from randomization to death due to any cause, will be analyzed using the Kaplan-Meier estimator of the survival function and the log-rank test of the null hypothesis of equal hazard functions, stratified by age group and region. The p-value of the two-sided log-rank test with significance level of 5% will be presented along with plots of the estimated survival functions for the two treatment groups, stratified by age group and region. The treatment effect of degarelix will be further examined by fitting a stratified Cox regression model for the time to death from any cause. The model will include treatment as a factor, be adjusted for the baseline CV risk factors as appropriate and stratified by age-group and region. The 95% confidence limits and associated p-value for the hazard ratio comparing treatment with degarelix to leuprolide will be presented.

TLF Table: Secondary Endpoint: Time to Death Due to Any Cause – FAS

TLF Figure: Survivor Function for Time to Death Due to Any Cause – FAS

9.3.5 Time from Randomization to confirmed (adjudicated) Cardiovascular-Related Death

Time from randomization to adjudicated CV-related death, is defined as the number of days from randomization to the date of the adjudicated CV-related death. The cause of death will be adjudicated by the external independent CEC Committee. Undetermined deaths will be presumed and analyzed as non-cardiovascular deaths. In order to correctly assess the treatment effect associated with degarelix with respect to the time to CV-related death, it is necessary to account for the competing risk, death due to other causes. The time measured in days, from randomization to the adjudicated CV-related death, will be analyzed using the Nelson-Aalen estimator of the cumulative cause specific hazard function and the log rank test of the null hypothesis of equal cumulative cause specific hazard functions, stratified by age group and region. The p-value of the two-sided log rank test with significance level of 5% will be presented along with plots of the cumulative cause specific hazard functions for the two treatment groups, stratified by age group and region. The treatment effect of degarelix will be further examined by fitting a stratified Cox-type

regression model for the cause specific hazard function associated with CV-related death. The model will include treatment as a factor, be adjusted for the baseline CV risk factors as appropriate and stratified by age-group and region. The 95% confidence limits and associated p-value for the cause specific hazard ratio comparing treatment with degarelix to leuprolide will be presented.

TLF Table: Secondary Endpoint: Time to Adjudicated Cardiovascular-related Death – FAS

TLF Figure: Cumulative Cause Specific Hazard Function for Time to Adjudicated Cardiovascular-related Death – FAS

9.3.6 Time from Randomization to Failure in Progression-Free Survival

Progression-free survival (PFS) is a composite endpoint consisting of the following conditions:

- Death
- Radiographic disease progression defined as one or more new metastatic skeletal lesions observed on bone scan; one or more new metastatic extra-skeletal lesions at least 1.5 cm in greatest dimension visible on computed tomography or magnetic resonance imaging scan as confirmed by the Investigator.
- Introduction of additional therapy related to prostate cancer treatment including radiation, anti-androgens and second-line treatment. (ATC and MedDRA codes for disease progression are included in Appendix 3)
- PSA failure defined as the time from randomization to the second occasion (must be at least two weeks apart from the first and correspond to consecutive measurements) in which the PSA value fulfills the following criteria:
  I. An absolute increase of ≥ 5 ng/ml above nadir and
  II. An increase of ≥ 50 % of nadir

Time to PFS failure is therefore defined as the time, measured in days, from randomization to the first occurrence of one of the above composite endpoint criteria. Patients discontinuing from treatment/withdrawn from the study will be censored at the time of discontinuation/withdrawal. Time to PFS failure will be analyzed using the Kaplan-Meier estimator of the survival function, the Cox regression model for the hazard rate and the log-rank test of the null hypothesis of equal hazard functions, stratified by age group and region. The p-value of the two-sided stratified log-rank test with significance level of 5% will be presented along with plots of the estimated survival functions for the two treatment groups, stratified by age group and region. The estimated hazard ratio and the associated 95% confidence interval and p-value comparing the treatment with Degarelix to Leuprolide will also be presented.

TLF Table: Secondary Endpoint: Time to PFS Failure – FAS

TLF Figure: Survivor Function for Time to PFS Failure – FAS

9.3.7 Testosterone levels at day 28, 168 and 336 in patients treated with degarelix and leuprolide

The proportion of patients castrated at day 28, 168 and 336 will be presented by treatment group, along with the number of patients with testosterone measurements at each assessment. Castration is defined as testosterone levels ≤ 0.5 ng/mL. Further, the proportion of patients castrated at both day 28 and 168, as well as at all three visits will be presented along with the number of patients with assessments at each of the corresponding times. For patients discontinuing treatment during the trial, any testosterone data collected after the date of discontinuation will be excluded from the analysis.

TLF Table: Secondary Endpoint: Probability of testosterone levels remaining at castrate levels – FAS

9.3.8 Total number of Cardiovascular-Related Hospitalizations over the duration of the trial

The total number of CV-related hospitalizations over the duration of the trial is defined as the number of hospitalizations due to CV-related adverse events, observed during the 12 month follow-up period for each patient.

The number of CV-related hospitalizations will be analyzed using a negative binomial model. The dependent variable will be the number of CV-related hospitalizations. The model will include a factor variable for treatment, the baseline count of CV-related hospitalizations (if available) as a covariate and will be further adjusted by including the logarithm of the number of days of follow-up for each patient as an offset. The inclusion of the offset term systematically adjusts the estimate of the treatment effect for potential differences in the duration of follow-up between patients. The model will further be adjusted for age-group and region. The estimated treatment difference with a 95% confidence interval will be presented.

TLF Table: Secondary Endpoint: Number of CV-related hospitalizations over the duration of the trial – FAS

9.3.9 Total number of Coronary Artery By-Pass Grafting or Percutaneous Coronary Intervention Procedures over the duration of the trial

The total number of CABG or PCI procedures observed over the duration of the trial will be analyzed in the same manner as the total number of CV-related hospitalizations, outlined in Section 9.3.8.

TLF Table: Secondary Endpoint: Number of CABG or PCI over the duration of the trial – FAS

9.3.10 Total number of Cardiovascular-Related Emergency Room Visit Events Observed over the duration of the trial

The total number of CV-related ER visit events observed over the duration of the trial for each patient will be analyzed in the same manner as the total number of CV-related hospitalizations, outlined in Section 9.3.8.

TLF Table: Secondary Endpoint: Number of Cardiovascular-related emergency room visits over the duration of the trial – FAS

9.3.11 Difference in Quality Adjusted Life Year (QALY) During One Year of Treatment

The EQ-5D-5L questionnaire can be used to estimate the QALY. The QALY is a measure of the value of health outcomes. Since health is a function of length of life and QoL, the QALY was developed as an attempt to combine the value of these attributes into a single index number. The basic idea underlying the QALY is simple: it assumes that a year of life lived in perfect health is worth 1 QALY (1 Year of Life × 1 Utility value = 1 QALY) and that a year of life lived in a state of less than this perfect health is worth less than 1. The QALY is derived as a cumulative measure for the treatment duration as the AUC of the time versus the index value. The AUC will be calculated using the trapezoidal rule for each of the visits values in relation to the baseline.

A detailed derivation of the QALY:

1) The EQ-5D-5L health state is converted into a single index value. The index values are country specific and we will use the value sets for the USA (*http://www.euroqol.org/home.html.*).
2) The QALY at the end of the trial is derived as the cumulative AUC for the index value as a function of time during the 12 months of treatment. This will be calculated as:

$$AUC = \sum_{i=1}^{i} \left(\frac{index_{(i-1)} + index_i}{2} \right) \times Time_{(i-(i-1))}$$

Where i=1, 2 and 3 for the corresponding visits at month 6, 11 and 12. The value, i=0, corresponds to baseline.

Time is measured as the actual number of days from baseline date of EQ-5D to each of the post-baseline EQ-5D Questionnaire completion dates during the 12 month trial.

The QALY at Visit 13 will be calculated for any patients who have a non-missing baseline index value. That is, any patients who are missing the EQ5D index value at baseline will not have a QALY measurement. Last observation carried forward principle will be used for missing measurements at Visit 8 or Visit 13 using only post-baseline values. The EQ5D index value will be carried forward to the planned visit date in order to calculate the QALY at 12 months. For patients with missing index value at Visit 8, but with known index value either at Visit 13 or 14, the QALY will be calculated as the AUC from baseline up to the next known visit.

The mean QALY at the end of the trial (12 months [1 month=28 days]) will be summarized by treatment arm and compared using an analysis of covariance (ANCOVA) model, where the QALY is the dependent variable and adjusted for treatment, age-group and region respectively.

9.3.12 Change from Baseline in Mean Total and QoL International Prostate Symptom Score during One Year of Treatment

The severity of lower urinary tract symptoms (LUTS) will be investigated using the total IPSS score. IPSS is a questionnaire containing eight questions regarding incomplete emptying, frequency, intermittency, urgency, weak stream, straining and nocturia and one question relating to the quality of life. Each question is assigned a total score on a scale from 0 to 5. The total IPSS score is then calculated as the summation over the responses for question 1 to7.

The eighth question regarding QoL is in relation to urinary symptoms denoted IPSS-QoL. The response to this question is analyzed separately and not included in the IPSS total score.

Missing values will not be imputed for this endpoint. If responses are missing to one or more of questions 1-7, the IPSS total score is considered missing as well. Results will be presented based on the observed cases.

Changes from baseline in the IPSS total score and QoL score will be compared between treatments longitudinally using repeated measures analysis of covariance (ANCOVA) with the change from baseline as the dependent variable and the baseline score as a covariate, treatment, age-group, region and visit as factors, including treatment by visit interaction term, assuming the working correlation matrix has the unstructured form implemented in SAS PROC MIXED. Based on the repeated measures ANCOVA model, the two-sided 95% confidence limits of the adjusted treatment contrasts and associated p-values will be provided.

TLF Table: Secondary Endpoint: IPSS – FAS

9.3.13 Change from Baseline in the Mean Duke Activity Status Index and Cardiac Anxiety Questionnaire Score during One Year of Treatment

The DASI and CAQ will be assessed at baseline (Visit 2), Visit 8, 14 and at the End-of-Trial visit. The change from baseline in DASI total score as well as CAQ total and domain scores will be compared between treatments longitudinally using repeated measures ANCOVA with the change from baseline as the dependent variable and the baseline score as a covariate, treatment, age-group, region and visit as factors, including treatment by visit interaction term, assuming the working correlation matrix has the unstructured form implemented in SAS PROC MIXED. Based on the ANCOVA model, the two-sided 95% confidence limits of the adjusted treatment contrasts and associated p-values will be provided.

TLF Table: Secondary Endpoint: The change in the mean DASI Score during one-year of treatment- FAS

TLF Table: Secondary Endpoint: The change from baseline in the mean CAQ Score during one-year of treatment – FAS

9.4 Exploratory Endpoints

9.4.1 Time from First Adjudicated MACE to Second Confirmed Adjudicated MACE

The exploratory efficacy endpoint, time from the first adjudicated MACE to a second confirmed (adjudicated) occurrence of the composite MACE endpoint, is aimed at further investigating the risk of CVD outcomes among prostate cancer patients treated with degarelix or LHRH agonist.

Only patients who have experienced one non-fatal MACE, will be considered at risk for a second MACE. The event time of interest will be the number of days from the first adjudicated non-fatal MACE until the second MACE. The endpoint will be analyzed via a Cox-type proportional intensity model. In essence the analysis is akin to the proposed conditional analysis of (Prentice, 1981) with a modification made based on the definition of the composite MACE endpoint. The model will include treatment as a factor, be [redacted], as well as stratified by age-group and region. Based on the Cox-type proportional intensity model, the two-sided 95% confidence limit of the adjusted relative rate for the treatment effect of degarelix compared to leuprolide will be provided alongside the associated p-value. Significant results will be interpreted cautiously, as randomization will not provide protection against imbalances between the two groups in potential confounders that are not explicitly adjusted for in the model. The treatment effect of degarelix compared to leuprolide with respect to the rate of MACEs will be further explored via an Andersen-Gill model (Andersen and Gill, 1982). The risk set for the Andersen-Gill model includes all patients who are under observation and at-risk for a MACE, i.e. the Andersen-Gill model incorporates information from all observed MACEs. [redacted]

Pseudo SAS code for implementing Andersen-Gill model

```
PROC PHREG DATA=<DATA> COVS(AGGREGATE);
    MODEL (TSTART, TSTOP)*CNSR(1) = ARMN;
  ID=USBJID;
RUN;
```

Note, in the above SAS code for the Andersen-Gill model, the robust standard errors are calculated by including the COVS(AGGREGATE) statement in the first line. Alternatively, model based standard errors could be returned by replacing the COVS(AGGREGATE) option with COVM.

TLF Table: Exploratory Endpoint: Time From First Non-Fatal adjudicated MACE to a Second Confirmed Occurrence of a MACE – FAS

[redacted]

10 Safety

10.1 General Considerations

Safety parameters will be evaluated for the safety dataset.

10.2 Adverse Events

Adverse events will be coded using MedDRA version 17.1 or later.

For adverse events, missing values will be treated as missing, except for causality, intensity, seriousness, and outcome of adverse events. A worst-case approach will be used: if causality is missing, the adverse event will be regarded as related to the IMP; if the intensity of an adverse event is missing, the adverse event will be regarded as severe; if seriousness is missing, the adverse event will be regarded as serious; if onset date is missing, it will be assumed to be the first day of dosing; if outcome is missing, and no date of outcome is present, the outcome is regarded as 'Not Recovered'.

An adverse event with the causal relationship to IMP judged as 'No reasonable possibility' is categorized as unrelated to IMP. An adverse event with the causal relationship to IMP judged as a 'reasonable possibility' is categorized as related to IMP and as an adverse drug reaction.

Treatment-emergent adverse events will be presented in summary tables and listings. The definition of a treatment-emergent adverse event is provided in Section 10.2.1.

10.2.1 Overview of Treatment-Emergent Adverse Events

Adverse events will be regarded as 'pre-treatment' if they occur between screening and the initial injections with IMP. Adverse events which occur in the time interval from initial dosing to 3 months after (1 month=28 days) last dosing of IMP will be considered to be 'treatment-emergent'. Adverse events will be regarded as 'post-treatment' if they occur 3 months (1 month=28 days) or more after the last dosing of IMP.

An adverse event overview summary table will be prepared including the number of patients reporting an adverse event, the percentage of patients (%) with an adverse event, and the number of events (E) reported, for the following categories:

- Treatment-emergent adverse events
- Deaths
- Serious adverse events
- Adverse events leading to withdrawal
- Severe and life threatening adverse events
- Adverse drug reactions

TLF Table: Overall summary of treatment-emergent adverse events – Safety

10.2.2 Incidence of Adverse Events

Treatment-emergent adverse events will be summarized in a table by MedDRA SOC and Preferred Term (PT). The Table will display the total number of patients reporting an adverse event, the percentage of patients (%) with an adverse event, and the number of events (E) reported. Adverse events will be presented by SOC sorted alphabetically and PT sorted in decreasing frequency of occurrence.

For each treatment the following counts are done:

- For number of patients experiencing a particular event, counting will be done by patient and not by event. This is valid for both SOC and PT, i.e., a patient will only be counted once in each SOC and once within each PT.
- For total number of events, counting will be done by event. This is valid for both SOC and PT, i.e., an event occurring more than once for the same patient will be counted for each occurrence.

Summary tables will be prepared for:

- All adverse events
- Adverse events with an incidence [≥5%] of patients in any treatment group
- Adverse events by causality (related/unrelated)
- Adverse events leading to death
- Adverse events by intensity
- Serious adverse events
- Adverse events leading to withdrawal

Supporting data listings will be provided for:

- All adverse events sorted by center and patient no.
- All adverse events sorted by MedDRA PT
- Serious adverse events
- Adverse events leading to death
- Adverse events leading to withdrawal.

In addition, tables summarizing all the treatment-emergent adverse events by MedDRA SOC and PT displaying the total number of patients reporting an adverse event, the percentage of patients (%) with an adverse event, and the number of events (E) reported will be provided.

TLF Table: Incidence of all adverse events by MedDRA System Organ Class and Preferred Term – Safety Analysis Set

TLF Table : Incidence of treatment-emergent non-serious adverse events (>5% cut-off) by MedDRA System Organ Class and Preferred Term – Safety Analysis Set

TLF Table: Incidence of all adverse events by causality, MedDRA System Organ Class and Preferred Term – Safety Analysis Set

TLF Table: Incidence of adverse events leading to death by MedDRA System Organ Class and Preferred Term – Safety Analysis Set

TLF Table: Incidence of all adverse events by intensity, MedDRA System Organ Class and Preferred Term – Safety Analysis Set

TLF Table: Incidence of serious adverse events by MedDRA System Organ Class and Preferred Term – Safety Analysis Set

TLF Table: Incidence of adverse events leading to withdrawal by MedDRA System Organ Class and Preferred Term – Safety Analysis Set

TLF Table: Incidence of treatment-emergent adverse events by MedDRA System Organ Class and Preferred Term – Safety Analysis Set

TLF Table: Incidence of treatment-emergent adverse drug reactions by MedDRA System Organ Class and Preferred Term - Safety Analysis Set

TLF Table: Incidence of treatment-emergent adverse events leading to discontinuations by MedDRA System Organ Class and Preferred Term - Safety Analysis Set

TLF Table: Incidence of treatment-emergent serious adverse events by MedDRA System Organ Class and Preferred Term – Safety Analysis Set

TLF Listing: Listings of all adverse events sorted by center and patient no.

TLF Listing: Listings of all adverse events sorted by MedDRA Preferred Term

TLF Listing: Listings of all serious adverse events

TLF Listing: Listings of all adverse events leading to death

TLF Listing: Listings of all adverse events leading to withdrawal

10.3 Safety Laboratory Variables

Baseline for all laboratory analyses will be the values obtained at the last assessment prior to the first dose of the IMP. Treatment-emergent laboratory data will include tests completed after the first dose of IMP through the residual time of drug effect. End of trial will include the last post-baseline observation during the trial.

[redacted]

10.3.1 Summary Statistics

Mean change and mean percentage (%) change from baseline to the end of trial will be presented for each laboratory variable. In addition, descriptive statistics, i.e., the number of patients with data,

mean (standard deviation), median, minimum, and maximum values, will be presented for observed values and change from baseline at each time-point for each laboratory variable.

[redacted]

10.3.2 Laboratory Variable Changes Relative to Normal Range

Changes relative to normal ranges are presented with shift tables with total number of patients, and number and percent of patients who experienced a shift by treatment group and period. The following categories for shift tables are defined:

- Low: Values which are below the lower reference range limit;
- Normal: Values which are within the lower and upper reference range;
- High: Values which are above the upper reference range limit.
- Absent: No value for measured variable (for urinalysis only)
- Present: Any value obtained for measured variable (for urinalysis only)

For all hematology and clinical chemistry variables, shift tables will be prepared to compare baseline values to the worst in-treatment value. More specifically, for hematology and clinical chemistry, tables presenting the changes from *Low* or *Normal* to *High* and from *High* or *Normal* to *Low* will be provided. For urinalysis variables, shift tables will summarize the number (%) of patients who had "absent" values at baseline and "present" values during the treatment period.

TLF Table: Incidence of hematology laboratory variable changes relative to normal range – Safety Analysis Set

TLF Table: Incidence of chemistry laboratory variable changes relative to normal range – Safety Analysis Set

TLF Table: Incidence of urinalysis variable changes relative to normal range – Safety Analysis Set

10.3.3 Data Listings

Data listings will be prepared by treatment group and center for all patients with any abnormal laboratory value at any time-point (including screening, baseline).

TLF Listing: Patients with abnormal laboratory measurements

10.3.4 Urinalysis

Incidence of changes in urinalysis will be summarized by treatment. A summary table with number of patients with change from *Absent* at baseline to *Present* during trial will be summarized.

TLF Table: Incidence of changes from baseline in urinalysis measurements during the trial – Safety Analysis Set

10.4 Vital Signs

10.4.1 Vital Signs

Baseline for all vital signs analyses will be the values obtained at the last assessment prior to the first dose of IMP. Treatment-emergent vital signs data will include tests completed after the first dose of IMP through the time of residual drug effect. End of trial will include the last post-baseline observation during the trial.

10.4.1.1 Summary Statistics

Mean change and mean percentage (%) change from baseline at end of trial will be presented for each vital signs variable. In addition, descriptive statistics, i.e., the number of patients with data, mean (standard deviation), median, minimum, and maximum values, will be presented for observed values and change from baseline at each time-point for each vital signs variable.

TLF Table: Summary of vital signs parameters by visit – Safety Analysis Set

10.4.1.2 Markedly Abnormal Changes

Summary tables will be prepared displaying the number and percentage of patients with normal baseline values who had one or more pre-specified markedly abnormal treatment-emergent value, as defined in Appendix 1.

TLF Table: Incidence of Markedly abnormal vital signs measurements– Safety Analysis Set

10.4.1.3 Data Listings

Data listings will be prepared by center for all patients with any abnormal vital signs value at any time-point (including screening, baseline).

TLF Listing: Patients with Markedly abnormal vital signs measurements

11 Interim Analysis

As the trial was terminated early due to feasibility reasons, planned interims analyses have been cancelled.

12 Deviations from Protocol Analysis

List of key secondary endpoints has been revised and testing procedure changed from Holm's to fixed-sequence.

Due to the trial being terminated early due to feasibility reasons, the statistical analysis plan has been reduced. See change log for details.

13 References

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14 Tables, Listings and Figures

An overview of the tables, listings and figures (TLFs) to be produced is provided in a separate document.

Appendix 1 Markedly Abnormal Vital Signs and Electrocardiograms (ECGs)

Table 2 Markedly abnormal Criteria for Vital Signs*

Variable	Criterion Value	Change from Baseline
Systolic blood pressure	≥ 180 mmHg ≤ 90 mmHg	Increase of ≥ 20 mmHg Decrease of ≥ 20 mmHg
Diastolic blood pressure	≥ 105 mmHg ≤ 50 mmHg	Increase of ≥ 15 mmHg Decrease of ≥ 15 mmHg
Pulse rate	≥ 120 bpm ≤ 50 bpm	Increase of ≥ 15 bpm Decrease of ≥ 15 bpm
Body weight	None	Increase of ≥ 7% Decrease of ≥ 7%
Body temperature	≥ 38.3° C	Increase to ≥ 39.4°C

* To be identified as markedly abnormal, a treatment value must meet the criterion value and also the specified change from baseline.

Table 3 Abnormal Criteria for Quantitative ECG Data

Variable	Baseline	Abnormal Treatment-Emergent Value
ECG heart rate	Normal	≤ 50 bpm and decrease from baseline of ≥ 15 bpm ≥ 120 bpm and increase from baseline of ≥ 15 bpm
Duration of PR interval	Normal	≥ 220 msec
Duration of QRS interval	Normal	≥ 120 msec
Duration of QTc interval	Normal	≥ 450 msec
Duration of QTc interval	Normal	≥ 480 msec
Duration of QTc interval	Normal	≥ 500 msec
Duration of QTc interval	Not applicable	Increase from baseline of ≥ 30 msec
Duration of QTc interval	Not applicable	Increase from baseline of ≥ 60 msec

Appendix 2 SMQs for AE Medical History of Special Interest

Table 4 Cardiovascular Events

SMQ	SMQ code
Myocardial infarction	20000047
Ischaemic central nervous system vascular conditions	20000063
Haemorrhagic central nervous system vascular conditions	20000064
Embolic and thrombotic events, arterial	20000082
Other ischaemic heart disease	20000168

Table 5 Diabetes Events

SMQ	SMQ code
Hyperglycaemia/new onset diabetes mellitus	20000041

Appendix 3 ATC codes and MedDRA terms for disease progression

A list of ATC codes for antiandrogens and additional therapies classified as disease progression are defined below. Please note that the list may be non-extensive.

Table 6 ATC Codes for Antiandrogens

Level 5 codes
L02BB01 Flutamide
L02BB02 Nilutamide
L02BB03 Bicalutamide
L02BB04 Enzalutamide
G03HA01 Cyproterone

Table 7 ATC codes for Additional Therapy

Level 5 codes
L01DB07 Mitoxantrone
L01CD02 Docetaxel
L01XX11 Estramustine
L01CD01 Paclitaxel
L02AA01 Diethylstilbestrol
L02AA02 Polyestradiol phosphate
L02AA03 Ethinylestradiol
L02AA04 Fosfestrol
L02AB01 Megestrol
L02BG01 Aminoglutethimide
L02BX03 Abiraterone
G01AF11 Ketoconazole

Investigators recording of disease progression are marked as a tick-box on the Adverse Event form in the eCRF. The MedDRA terms to be used for radiation and second line treatment are defined below.

Table 8 MedDRA Codes (preferred terms) for Radiation

10006089	Brachytherapy to prostate	PT
10014442	Electron radiation therapy to prostate	PT
10017683	Gamma radiation therapy to prostate	PT
10034955	Photon radiation therapy to prostate	PT
10061544	Radiotherapy to prostate	PT
10048205	X-ray therapy to prostate	PT
10014435	Electron radiation therapy to bone	PT
10017675	Gamma radiation therapy to bone	PT
10034947	Photon radiation therapy to bone	PT
10062089	Radiotherapy to bone	PT
10048197	X-ray therapy to bone	PT

Table 9 MedDRA Codes (preferred terms) for Second Line Treatment

10061916	Prostatectomy	PT
10050756	Radical prostatectomy	PT
10038961	Retro-pubic prostatectomy	PT
10042594	Suprapubic prostatectomy	PT
10044445	Transurethral prostatectomy	PT

The following terms are also to be classified as investigators recording of disease progression, in case the investigator did not check the tick-box, but only recorded the AE.

Table 10 MedDRA Codes (preferred terms) for additional classification of investigators recording of disease progression

10010264	Condition aggravated	PT
10061818	Disease progression	PT
10061819	Disease recurrence	PT
10048669	Terminal state	PT
10051398	Malignant neoplasm progression	PT
10027452	Metastases to bone	PT
10027459	Metastases to lymph nodes	PT
10027457	Metastases to liver	PT
10027458	Metastases to lung	PT
10027463	Metastases to pleura	PT
10062194	Metastasis	PT

Appendix 4 ATC codes and MedDRA terms for Prohibited Therapy

A list of ATC codes for prohibited concomitant medication are defined below. Please note that the list may be non-extensive.

Table 11 ATC codes for prohibited concomitant medication

Level 5 codes
L02AB01 Megestrol acetate
G01AF11 Ketoconazole
L02BX03 Abiraterone
L02BB04 Enzalutamide
L02BB01 Flutamide
L02BB02 Nilutamide
L02BB03 Bicalutamide
G03HA01 Cyproterone
L02AA01 Diethylstilbestrol
L02AA02 Polyestradiol phosphate
L02AA03 Ethinylestradiol
L02AA04 Fosfestrol

Additionally all substances in the ATC G03 therapeutic subgroup are considered as prohibited concomitant medications.

Table 12 MedDRA code (preffered term) for prohibited therapy

10049628	Bilateral orchidectomy	PT

Appendix 5 Cardiovascular Endpoint Definitions

Endpoints / Event definitions

The cardiovascular endpoint definitions given below are based on the 2014 Definitions for Cardiovascular Endpoint Events in Clinical Trials[1].

1.1 Death

All deaths will be categorized as Cardiovascular, non-Cardiovascular or Undetermined.

Cardiovascular Death: Cardiovascular Death is defined as death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular procedures, death due to cardiovascular hemorrhage, and death due to other cardiovascular causes.

Non-cardiovascular Death: Non-cardiovascular death is defined as any death that is not thought to be due to a cardiovascular cause (e.g. cancer related death). Non-cardiovascular deaths will also be sub-classified as related to prostate cancer progression or to other causes.

Undetermined Cause of Death: Undetermined cause of death refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause, due to absence of any information (e.g., the only available information is "patient died"). Undetermined death will be presumed and analyzed as non-cardiovascular deaths on the secondary analysis.

1.2 Myocardial Infarction

The adjudication of myocardial infarction as a clinical endpoint will consider the occurrence relative to a percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG). (It will also be consistent with the revised American College of Cardiology (ACC) / European Society of Cardiology (ESC) myocardial infarction definition document.)

In the absence of a PCI or CABG, a spontaneous myocardial infarction is defined as:

[redacted]

For patients having a PCI, a myocardial infarction will be defined as:

CK-MB (or troponin I/T or CK in the absence of CK-MB) >3 x ULN for samples obtained within 24 hours of the procedure if the baseline values were normal or at least a 50% increase

over elevated baseline values that were stable or decreasing or development of new pathological Q waves (>0.04 seconds) in at least 2 contiguous leads in the absence of LBBB on the ECG. Symptoms of cardiac ischemia are not required.

After CABG surgery, a myocardial infarction is defined as either:

CK-MB (or CK in the absence of CK-MB) >5 x ULN for samples obtained within 24 hours of the procedure with development of new pathological Q waves in at least 2 contiguous leads in the absence of LBBB on the ECG.

CK-MB (or CK in the absence of CK-MB) >10 x ULN for samples obtained within 24 hours of the procedure with or without development of new pathological Q waves in at least 2 contiguous leads in the absence of LBBB on the ECG.

Note: For institutions that report an 'intermediate' or 'equivocal' range for biomarker elevation that is not definitively associated with myocardial necrosis or infarction then the ULN should be the lower value for the necrosis or infarct range, not the 'equivocal' or 'intermediate' range lower value.

1.3 Unstable Angina Requiring Hospitalization

[redacted]

1.4 Cerebrovascular Accident (Stroke)

Stroke is defined as an acute focal neurological deficit of sudden onset that is not due to an identifiable non-vascular cause (i.e. brain tumor, trauma, brain procedures, metabolic condition)

a) that is not reversible within 24 hours or results in death (in <24 hours)

or

b) that resolves in<24 hours and is accompanied by clear evidence of a new stroke on cerebral brain imaging studies (brain Computed tomography [CT] or Magnetic Resonance Imaging [MRI] scans)

Classification:

Ischemic Stroke: is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by central nervous system (CNS) infarction.

Note: Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

Hemorrhagic Stroke: is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

Note: Subdural hematomas without new neurologic symptoms are intracranial hemorrhagic events and not strokes.

Undetermined Etiology: is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as either ischemic or hemorrhagic.

[1] Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, et al. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). J Am Coll Cardiol 2015 Jul 28;66(4):403-69.