FERRING
PHARMACEUTICALS

Protocol

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: 26 Mar 2021

CLINICAL TRIAL PROTOCOL

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)

000108

EudraCT Number:	2017-002495-20
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
Name and Address of Sponsor:	Ferring Pharmaceuticals A/S Clinical R&D, Urology [redacted] Denmark Tel. [redacted]
Version:	7.0 (consolidated protocol; changes to protocol 6.0 introduced with amendment #07 implemented)
GCP Statement:	This trial will be performed in compliance with GCP.

SYNOPSIS

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)

SIGNATORY INVESTIGATORS

[redacted] Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[redacted] Division of Cardiology, Duke University Medical Center, Durham, NC, USA

TRIAL SITES

Approximately 70 trial sites will be opened in the USA and Canada. At the time of the interim analysis, or if the recruitment rate is lower than expected, additional sites in other countries may be opened.

PLANNED TRIAL PERIOD	CLINICAL PHASE
First patient first visit (FPFV) expected Q1 2016 Last patient last visit (LPLV) expected Q2 2021	3b

OBJECTIVES

Primary Objective

- The primary objective is to assess the effect of a gonadotropin-releasing hormone (GnRH) receptor antagonist (degarelix) on the risk of occurrence of major adverse cardiovascular events (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 cardiovascular disease (CVD)

Secondary Objectives

The secondary objectives are:

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) or 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 Days 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 (CT) 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 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 5 Levels 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

Exploratory Objectives

The exploratory objectives are:

- 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]

ENDPOINTS

Primary Endpoint

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

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

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]

METHODOLOGY

Trial Design

This is a multi-center, randomized, assessor-blind, controlled trial to compare the occurrence of 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 21 days prior to randomization for compliance with the inclusion and exclusion criteria.

Patients will be randomized to one of the two treatments in a 1:1 ratio stratified by baseline age group and region. Patients should be evaluated by a CV specialist to ensure that their CVD treatment is according to standard-of-care before trial entry. Cardiovascular disease information and source medical documents will be requested by the Investigator from the patient's CV specialist to

evaluate and document CVD history for eligibility, using a Medical / CV History Request Form. A process will be implemented for the collection and review of supporting source data (with the involvement of the contract research organization [CRO] and Duke Clinical Research Institute [DCRI]) to ensure the accuracy of patients' medical records documentation for the CVD-related inclusion criteria. The Investigator should ensure that pre-existing CVD and any CVD that may be diagnosed during the trial is managed by a CV specialist according to standard clinical practice. After randomization, the management of CVD and prostate cancer is intended to reflect standard-of-care. Monitoring for MACEs will occur throughout the trial applying a specific Clinical Events Classification (CEC) process ensuring blinding of the assessors. Adjudication of MACEs will be performed by an external independent blinded CEC Committee (see Trial Committees below). Trial visits are scheduled to occur monthly until trial end.

Treatment

Patients randomized to degarelix will receive a starting dose of 240 mg degarelix (two subcutaneous [s.c.] injections, each of 120 mg) followed by up to 11 single monthly (28-day intervals) s.c. injections of 80 mg degarelix, according to the approved dosing regimen. Patients randomized to leuprolide will receive one dose (22.5 mg leuprolide), administered intramuscularly (i.m.), every 3 months (84-day intervals) according to label recommendations, up to a total of 4 doses.

In line with inclusion criterion No. 4 (see Criteria for Inclusion / Exclusion below), investigators and patients are encouraged to continue investigational medicinal product (IMP) treatment during the entire duration of the trial, unless clinical progression or medical status indicate otherwise at the discretion of the Investigator.

Adverse Events, Cardiovascular-Related Recordings and other Safety Assessments

Adverse events will be recorded from the time point of obtaining signed informed consent until the End-of-Trial visit. Adverse events that occur before administration of the first dose of IMP will be regarded as pre-treatment adverse events.

The sources of adverse events cover:

- The patient's response to general questions about his health (a standard non-leading question such as "How have you been feeling since your last visit?" is asked at each visit)
- Symptoms spontaneously reported by the patient
- Investigations and examinations where the findings are assessed by the Investigator to be clinically significant changes or abnormalities
- Other information relating to the patient's health becoming known to the Investigator

CV-related adverse events and any worsening in CV status will be collected from Visit 2 until the End-of-Trial visit. The sources of CV-related information cover:

- Admission to hospital or ER since last visit

- Death
- Admission for chest pain (ischemic) symptoms that could be an unstable angina or myocardial infarction event
- Admission for new neurological symptoms that could be a cerebrovascular (stroke) event
- Any drawn creatinine kinase (CK), creatine kinase-muscle brain (subunit) (CK-MBs) or troponin samples since last visit

The information obtained should be entered in the electronic case report form (eCRF). In case pre-defined items on the eCRF checklist are answered affirmatively, a specific clinical endpoint form in the eCRF relating to each of the questions that were answered "yes", must be completed by the site personnel.

In case of any suspected CV-related adverse events, further examination of CV status will be performed. Data on suspected CV-related adverse events and related medical documentation will be collected and delivered to the CEC Committee before the adjudication of MACEs takes place (see Trial Committees below).

The Investigator should ascertain that patients are evaluated by a CV specialist and treated according to standard-of-care for their pre-existing CVD and any CVD that may be diagnosed during the trial.

A physical examination will be performed at screening (Visit 1) and at the End-of-Trial visit. Vital signs (pulse and blood pressure) will be assessed at all visits. Blood samples for assessment of safety laboratory variables (clinical chemistry and hematology), as well as urine samples for urinalysis, will be collected at screening (Visit 1), at baseline (Visit 2) and at the End-of-Trial visit (Visit 14). In addition, blood samples for assessment of clinical chemistry will be collected at Visits 3 and 8 to allow for periodic safety monitoring for QT prolongation. [redacted] Data on suspected CV-related vital signs and laboratory findings will be delivered to the CEC Committee before the adjudication of MACEs takes place.

A 12-led electrocardiogram (ECG) recording will be performed at baseline (Visit 2), Visits 3, 8 and at the End-of-Trial visit (Visit 14). In case of a CV event, additional ECG recordings may be performed at the discretion of the Investigator. Assessments of vital signs, baseline ECG recording, blood sampling, and urine collection must be performed prior to dosing.

Concomitant medications will be recorded at all visits and drug accountability will be recorded from Visit 2 and throughout the trial.

Blood Samples for Serum Testosterone and Prostate-Specific Antigen

Blood samples for monitoring of serum testosterone levels will be collected at screening (Visit 1), at Visits 3 and 8 and at the End-of-Trial visit (Visit 14).

Blood samples for analysis of PSA, as part of the PFS endpoint, will be collected at screening (Visit 1), at baseline (Visit 2), and every 3 months until the End-of-Trial visit (Visit 14).

Health Economics and Patient Reported Outcomes

Health care resource use will be recorded by appointed trial personnel (e.g. trial nurse) at each visit from Visit 2 until the End-of-Trial visit (Visit 14). The patient reported outcome (PRO) questionnaires EQ-5D-5L, DASI and CAQ will be completed by the patient at baseline (Visit 2), at Visit 8 and at the End-of-Trial visit (Visit 14). The IPSS questionnaire will be completed by the patient at baseline (Visit 2) and at Visits 5, 8 and 11 and at the End-of-Trial visit (Visit 14).

Trial Committees

Three committees with specific roles and responsibilities will be established for the trial:

- CEC Committee
- Data and Safety Monitoring Board (DSMB)
- Steering Committee

An external independent CEC Committee will be established to provide an independent and blinded adjudication and classification of CV events throughout the trial. The CEC Committee will consist of 3 selected cardiology experts (including 1 chair), 1 neurology expert and 1 oncology expert not otherwise involved in the trial. In addition, 1 project leader and 1 coordinator at DCRI will support the CEC Committee activities. The complete adjudication process, including responsibilities and the composition of the CEC Committee, the schedule and format of the meetings, and the data to be evaluated are presented in a separate CEC charter. The adjudicated MACEs will be used for the primary endpoint analysis. Adjudicated MACE data will be transferred directly from the CEC Committee to the DSMB in order to keep those data blinded to the Sponsor.

The independent DSMB will consist of 1 chair, 1 voting independent statistician, 1 cardiologist and 1 urologist not otherwise involved in the trial. A non-voting statistician from the DSMB Independent Statistical Group (ISG) will attend DSMB meetings to present information and address questions related to the analyses. The major purpose of the DSMB is to periodically evaluate safety data throughout the trial period. An additional purpose of the DSMB is to perform a pre-planned unblinded interim analysis, assessing the treatment-related hazard ratio and event rates of the adjudicated MACEs. The responsibilities and the composition of the DSMB, the schedule and format of the meetings, the voting procedures, and the data to be evaluated are described in a separate charter document.

The DSMB will perform one pre-planned and unblinded interim analysis of the primary endpoint

and will, based on pre-specified criteria, make recommendations to the Steering Committee whether to continue as is, to modify (increase the sample size) or to stop the trial due to futility according to predetermined criteria (outlined in the Statistical Analysis Plan [SAP] and the DSMB charter).

The Steering Committee will consist of external experts (as a minimum a statistician, a cardiologist and a urologist) and a Sponsor representative who is not part of the trial team. The Steering Committee will be responsible for trial integrity and decisions related to the trial, such as protocol amendments, and decisions based on interim recommendations by the DSMB as to whether the trial is to be stopped, to be continued, or sample size is to be increased.

Withdrawal and Follow-Up

A patient who prematurely discontinues treatment with IMP should be called in for an end-of-treatment visit as soon as possible (within 30 days) after a decision of treatment discontinuation has been taken. The reason for premature IMP discontinuation should be recorded in the eCRF. The patient should then be contacted by telephone each month throughout the trial period for collection of follow-up information on hospitalizations and potential CV events, and concomitant medication. At the end of the trial, i.e. after 336 days of participation in the trial, the patient should be called in for an end-of-trial visit.

In case a patient is lost to follow-up, all attempts have to be made to obtain the vital and medical status of the patient at the planned end-of-trial for the patient.

NUMBER OF PATIENTS

Approximately 900 patients are planned to be randomized in a 1:1 ratio to treatment with either degarelix or leuprolide. The randomization will be stratified by baseline age group (<75 and ≥75 years of age) and region (North America and Other regions).

CRITERIA FOR INCLUSION / EXCLUSION

Inclusion Criteria

Each patient must meet the following inclusion criteria before entry into the trial:

1. Signed informed consent obtained before any trial-related activity is performed.
2. Histologically confirmed adenocarcinoma of the prostate.
3. Clinical tumor staging (Tumor, Nodule and Metastasis [TNM]) available prior to treatment start; radiographic imaging (bone scan and/or CT scan and/or MRI) performed within 3 months prior to randomization. If no radiographic image is available at the time of screening, a bone scan should be performed.
4. Investigator judgment to initiate continued androgen deprivation therapy (ADT) with an intended treatment duration of 12 months or longer including any of the following disease categories:

A. Patients with metastatic prostate cancer at the time of diagnosis.

B. Patients with prostate cancer who develop metastases after local therapy.

C. Patients with prostate cancer with very high-risk, high-risk or intermediate-risk disease with features of unfavourable prognosis who are going to be treated with definitive radiation therapy in combination with at least 12 months of neoadjuvant/adjuvant ADT.

D. Patients with biochemical recurrence after local therapy who have a PSA doubling time <12 months.

E. Patients previously treated with definitive local therapy (without ADT combination) who due to risk features such as positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA, will be treated with salvage radiation therapy in combination with neoadjuvant/adjuvant ADT that is planned for 12 months or longer.

F. Patients with locally advanced prostate cancer who are not candidates (who are unsuited) for definitive therapy with surgery or radiation and will be treated with primary ADT.

5. Patients must be treatment-naïve with regard to ADT at time of randomization (with the exception of prior history of neoadjuvant/adjuvant ADT to definitive therapy for which the last administration, e.g., injection of a depot ADT formulation was at least 12 months prior to randomization).

6. Patients must have a screening serum testosterone level above the lower limit of normal range, defined as >150 ng/dL (5.2 nmol/L), apart from those who had prior neoadjuvant/adjuvant ADT (>12 months prior to randomization) where non-castrate range (>50 ng/dL or ≥1.73 nmol/L) should be applied.

7. Patients must have an Eastern Cooperative Oncology Group (ECOG) score of ≤2.

8. Pre-existing CVD (confirmed diagnosis prior to randomization) with **at least one** of the following criteria documented with applicable medical source documents:

A. Prior myocardial infarction ≥30 days before randomization.

B. Prior revascularization procedure ≥30 days before randomization, specified as any of the following:

- Coronary artery stent placement or coronary artery balloon angioplasty
- Coronary artery bypass graft surgery
- Stent placement or balloon angioplasty to a carotid, iliac, femoral, or popliteal artery
- Carotid endarterectomy surgery
- Vascular bypass surgery of the iliac, femoral, or popliteal arteries

C. Results from an angiogram or CT angiogram of the coronary, carotid, iliac,

femoral, or popliteal arteries that documented at least one vascular stenosis ≥50% at any time point before randomization.

D. Carotid ultrasound results that documented a vascular stenosis ≥50% at any time point before randomization.

E. Ankle-brachial pressure index (ABPI) <0.9 at any time point before randomization.

Exclusion Criteria

A patient who meets one or more of the following exclusion criteria cannot be included in this trial:

1. Previous or current hormonal management of prostate cancer (surgical castration or other hormonal manipulation, including GnRH receptor agonists, GnRH receptor antagonists, anti-androgens, estrogens, megestrol acetate, ketoconazole, abiraterone and enzalutamide); except neoadjuvant/adjuvant ADT (in this case treatment has to be terminated at least 12 months prior to randomization).
2. Hypersensitivity towards any component of the IMPs or excipients.
3. Uncontrolled type 1 or type 2 diabetes mellitus (defined as hemoglobin A_{1c} [HbA_{1c}] >10%) at time of randomization.
4. Uncontrolled hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg) at time of randomization.
5. A history of congenital Long QT Syndrome or risk factors for Torsade de Pointes ventricular arrhythmias (e.g. heart failure, hypokalemia, concomitant medication known to cause QT prolongation).
6. Myocardial infarction within 30 days prior to randomization.
7. Stroke (hemorrhagic or ischemic) within 30 days prior to randomization.
8. Coronary, carotid, or peripheral artery revascularization within 30 days prior to randomization.
9. Planned or scheduled cardiac surgery or PCI procedure that is known at the time of randomization.
10. Other clinically significant disorder (other than prostate cancer and CVD) including, but not limited to, renal, hematological, gastrointestinal, endocrine, neurological, or psychiatric disease, and alcohol or drug abuse or any other condition, which may affect the patient's health or the outcome of the trial as judged by the Investigator.
11. Mental incapacity or language barrier precluding adequate understanding or co-operation.
12. Treatment with an investigational drug within the last month prior to randomization or longer if considered to possibly influence the outcome of the current trial or planned or concurrent participation in a clinical trial for any investigational drug or device.

INVESTIGATIONAL MEDICINAL PRODUCTS

Degarelix (FIRMAGON)

Degarelix (FIRMAGON) powder and solvent for solution for injection 1-month depot.

Degarelix starting dose: Two s.c. depot injections containing 120 mg of degarelix each in 3.0 mL of sterile water (i.e. the starting dose will be 240 mg).

Degarelix maintenance dose: A single s.c. depot injection containing 80 mg of degarelix in 4.0 mL of sterile water. The maintenance dose will be administered monthly (28-day intervals) for the rest of the trial period. A treatment window of ±7 days is allowed.

Leuprolide acetate (LUPRON DEPOT 22.5 mg)

Leuprolide acetate (LUPRON DEPOT 22.5 mg) lyophilized microspheres and diluent for suspension for intramuscular (i.m.) injection according to label recommendations, every 3 months (84-day intervals) throughout the trial. A treatment window of ±7 days is allowed.

ADT will be restricted to degarelix and leuprolide to facilitate the comparison of CV risk in ADT-naïve prostate cancer patients. Concomitant treatment with anti-androgens (e.g. bicalutamide 50 mg once a day) for a maximum period of up to 28 days is allowed in metastatic patients requiring initial symptomatic flare protection at the discretion of the Investigator. Other ADTs (e.g. abiraterone) are prohibited during the trial.

DURATION OF TREATMENT

Each patient will be treated for 1 year (336 days i.e. 12 treatment months of 28 days each).

STATISTICAL METHODS

Sample Size Calculations

As suggested by a post-hoc analysis of degarelix safety data the 1-year event rates for a CV event or death due to any cause are 5.3% and 12.1% for degarelix and leuprolide, respectively, in the global patient population with prior CVD. This would correspond to an unadjusted hazard ratio of 0.42 (in comparison, the adjusted hazard ratio is 0.39 [95 % confidence interval = [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 1-year event rates 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 = [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 1-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.

Trial Design

One interim analysis is planned after 50% of the confirmed, adjudicated MACE endpoints have

been collected. The interim analysis will assess the hazard ratio, response rates of the adjudicated MACEs and reassess the sample size in the event that the stopping boundaries for futility are not crossed. The futility bound expressed in terms of the hazard ratio is 0.78. That is, if the observed hazard ratio is >0.78 the DSMB may suggest to stop the trial due to futility. The futility bounds are non-binding. Accounting for the possibility of stopping the trial early for futility, an alternative hypothesis of a hazard ratio of 0.49 and 80% power, 66 events are required at final analysis, corresponding to 876 patients, in order to reject the null hypothesis of equal hazards at the two-sided 5% Type I error level.

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 a close to zero spending of alpha at the interim analysis.

Adjustments for Sample Size Re-Estimation
The conditional power for different sample size increases will be evaluated at the interim using ADDPLAN™ 6. In case of a sample size increase, the final test statistics are adjusted by using the normal inverse method. This is done 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 S1.

Table S1 Sample Size Calculations (Number of Events Rounded Upwards)

Information Rate	Accept H_0			Reject H_0	α spent	Power Achieved	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

Statistical Analyses
Primary Analysis
The primary endpoint, the time from randomization to the first confirmed occurrence of the composite MACE endpoint in the two treatment groups, will be analyzed based on the Kaplan-Meier estimator of the survival function and the log-rank test stratified for age group and region.

The null hypothesis of equal hazard functions between the two treatment groups, will be rejected if the test statistics exceed the critical level for a two-sided hypothesis test with a Type I error level of 5%.

Conclusions on significance of the primary endpoint analysis will be based on the Full Analysis Set (FAS) censoring patients at the time of treatment discontinuation, initiation of prohibited therapies related to hormonal treatment, lost to follow-up/withdrawal from the trial or Day 336, whichever occurs first.

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

Key Secondary Analyses
The following analyses are included in the 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

Other Secondary Analyses
The remaining secondary endpoints will be tested outside the scope of the hierarchy; without adjustment for multiplicity.

- 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
- Testosterone levels at Days 28, 168 and 336 in the degarelix and leuprolide treatment groups
- Time from randomization to failure in PFS
- Total number of CV-related hospitalization events 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 the treatment period
- Changes from baseline in PRO instruments will be analyzed longitudinally across the treatment period (IPSS and EQ-5D-5L) and cross-sectionally (DASI and CAQ)

Laboratory data, vital signs, and adverse events data will be presented as appropriate.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

List of Abbreviations

ABPI	Ankle-Brachial Pressure Index
ADR	Adverse Drug Reaction
ADT	Androgen Deprivation Therapy
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
AV	Atrioventricular
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CABG	Coronary Artery by-pass Grafting
CAQ	Cardiac Anxiety Questionnaire
CEC	Clinical Events Classification
CK	Creatinine Kinase
CK-MB	Creatine Kinase-Muscle Brain (subunit)
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
CVD	Cardiovascular Disease
DASI	Duke Activity Status Index
DCRI	Duke Clinical Research Institute
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ePRO	Electronic Patient Reported Outcome
EQ-5D-5L	EuroQol Group 5 Dimensions 5 Levels Questionnaire
EQ VAS	EQ Visual Analogue Scale
ER	Emergency Room
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GnRH	Gonadotropin-Releasing Hormone
HbA_{1c}	Hemoglobin A_{1c}
HRQL	Health-Related Quality of Life
[redacted]	[redacted]
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
i.m.	Intramuscular(ly)

IMP	Investigational Medicinal Product
IPSS	International Prostate Symptom Score
IRB	Institutional Review Board
ISG	Independent Statistical Group
ITT	Intention-to-Treat
LPLV	Last Patient Last Visit
LUTS	Lower Urinary Tract Symptoms
MACE	Major Adverse Cardiovascular Event
MCHC	Mean Cell Hemoglobin Concentration
MCV	Mean Cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NIH	National Institutes of Health
NLM	National Library of Medicine
[redacted]	[redacted]
PCI	Percutaneous Coronary Intervention
PDF	Portable Document Format
PFS	Progression-Free Survival
PRO	Patient Reported Outcome
PSA	Prostate-Specific Antigen
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RBC	Red Blood Cell
REB	Research Ethics Board
ROC	Receiver Operating Characteristics
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
s.c.	Subcutaneous(ly)
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TNM	Tumor, Nodule and Metastasis
WBC	White Blood Cell
WHO	World Health Organization

Definition of Terms

Investigator	A Medical Doctor at the trial center responsible for the conduct of the clinical trial.
Sponsor	Ferring Pharmaceuticals A/S, Copenhagen, Denmark
Month	One treatment month is equal to 28 days/4 weeks
Trial-related Activity	Any procedure that would not have been performed during the normal management of the patient
Screened	Patient who has signed informed consent
Randomization	Patient is randomly assigned to a treatment group and given a unique patient number

1 INTRODUCTION

1.1 Background

The current management of advanced prostate cancer involves androgen deprivation therapy (ADT) (Medical Research Council Trial, 1997; Granfors, 1998; Messing, 1999). In general, suppression of the serum testosterone level to the desired therapeutic goal (≤0.5 ng/mL) can be achieved by surgical (bilateral orchiectomy) or medical castration including administration of gonadotropin-releasing hormone (GnRH) receptor agonists or GnRH receptor antagonists.

ADT is associated with a number of well-known side effects, such as sexual dysfunction, hot flashes, osteoporosis and metabolic changes that can lead to atherosclerosis (Nguyen, 2014; Allan, 2014).

A number of large-scale epidemiological studies have in post-hoc analyses found that treatment with GnRH receptor agonists is associated with a long-term increased risk of cardiovascular disease (CVD) (Smith, 2008; Basaria, 2008; Saigal, 2007), however, this association appears to be lacking or less consistent for bilateral orchiectomy or anti-androgen treatment. In many cases, cardiovascular (CV) events develop early after treatment initiation (<12 months and as early as after 1-4 months of exposure), which could suggest a short-term treatment related risk for aggravation or destabilisation of existing atherosclerotic vascular disease (Smith, 2008; Basaria, 2008; Tsai, 2007; Lester-Coll, 2013). This short-term risk raises concerns in patients with pre-existing CVD where the potential mechanism could go beyond the medical castration related metabolic changes. In line with this, studies have consistently shown that history of major CV events is a strong risk factor for subsequent CV complications during ADT therapy (D'Amico, 2007; Nanda, 2009).

Degarelix is a GnRH receptor antagonist that competitively binds to GnRH receptors in the anterior pituitary gland. The qualitative difference in the mechanism of action between GnRH receptor antagonists and GnRH receptor agonists, including the effect on the follicle-stimulating hormone (FSH) as well as potentially functional GnRH receptors identified in peripheral tissues e.g. T-lymphocytes, raises the possibility that GnRH receptor agonists and GnRH receptor antagonists may have different profiles with respect to short-term CV safety in patients with established CVD (Albertsen, 2014; Smith, 2011).

In the epidemiological studies which showed an increased risk of CV events, ADT was achieved with GnRH receptor agonists, and to a limited extent, anti-androgens. To-date, there is limited information as to whether GnRH receptor antagonists would carry similar CV risk.

1.2 Scientific Justification for Conducting the Trial

The CV safety of degarelix was evaluated throughout the clinical development programme with 1,836 prostate cancer patients exposed to degarelix. Of these, 775 patients were exposed to degarelix for more than one year. No general CV safety concerns were identified in the clinical trial

programme (Smith, 2011). More specifically, the potential effect of degarelix on prolongation of the QT interval was investigated in two controlled clinical trials. An analysis of data from the pivotal Phase 3 trial, FE 200486 CS21, demonstrated similar incidences of QT prolongation and arrhythmias for patients treated with degarelix or leuprolide (Smith, 2010). In addition, a Phase 1 thorough QTc evaluation trial in healthy adult males (FE 200486 CS22) investigated the intrinsic effect of degarelix on the QT/QTc intervals (Clinical Trial Report FE 200486 CS22, 2012). This trial demonstrated that degarelix did not have any intrinsic effect on prolongation of the QTcF interval, heart rate, atrioventricular (AV) conduction, or cardiac repolarization.

A non-comparative pooled analysis of CVD risk in 1,704 patients was performed to investigate associations of baseline CVD risk profile, dosing regimen and treatment duration with the incidence of CVD events during ADT with degarelix in patients with prostate cancer (Smith, 2011). Events were coded using Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) terms and grouped into one of the four categories used for the collection of medical history: ischemic heart disease, cerebrovascular disorders, arterial thrombotic/embolic events, and claudication. This safety analysis demonstrated that the incidence of CV events was similar before and after degarelix treatment and events were largely confined to men with a history of CVD.

In addition, a pooled analysis of data from six Phase 3/3b randomized, comparative trials (2,328 patients with prostate cancer treated with degarelix [n=1,491] and with GnRH receptor agonists [n=837]) was performed (Tombal, 2013; Albertsen, 2014). CV events were defined by any of the five MedDRA SMQs: myocardial infarction, ischaemic cerebrovascular conditions, haemorrhagic cerebrovascular conditions, embolic and thrombotic arterial events, and other ischaemic heart disease.

In brief, the analysis showed that significantly fewer patients treated with degarelix experienced a CV event or death of any cause compared with those receiving a GnRH receptor agonist. In patients with a medical history of CVD at baseline, the risk of experiencing a CV event or death was approximately 50% lower in the degarelix group. Hence, these data suggest that men, especially those requiring ADT and with a history of CVD, may experience a significantly lower risk of CVD sequelae when treated with degarelix compared with a GnRH receptor agonist.

The primary aim of the present safety trial is to prospectively evaluate short-term, drug-related CV risk by comparing the occurrence of major adverse cardiovascular events (MACEs) in patients with prostate cancer and concomitant CVD who receive degarelix or the GnRH receptor agonist leuprolide. In addition, a number of non-CV-related secondary endpoints will be studied with the purpose to further investigate the potential differences in the risk-benefit profile of degarelix versus GnRH receptor agonist.

[redacted] Currently the most widely used biomarker in prostate

cancer is prostate-specific antigen (PSA), which is a glycoprotein that is found almost exclusively in normal and neoplastic prostate cells. Many but not all investigators have observed an association between a decline in PSA levels of 50% or greater and survival. However, PSA is not always optimal as a single biomarker for prostate cancer diagnosis or progression. Recent development in e.g. proteomics and immunology offer new approaches to evaluate progression. The methods are not fully developed and more evidence is needed in terms of validation in prostate cancer patients.

[redacted]

1.3 Benefit / Risk Aspects

Treatment with degarelix or leuprolide is expected to be associated with benefits for the population of prostate cancer patients with concomitant CVD and in whom ADT is indicated, leading to delayed progression of prostate cancer or disease symptoms (Levine, 2010).

Agonists initially stimulate the pituitary GnRH receptors, resulting in a rapid increase in testosterone levels (surge), which might stimulate prostate cancer cells and delay the onset of ADT (Klotz, 2014; Carter, 2014). This may lead to an exacerbation of clinical complications such as bladder outlet obstructions, spinal cord compression, and bone pain (clinical flare) in patients with advanced disease. Degarelix competitively binds to the GnRH receptor and promptly blocks testosterone production, resulting in a rapid (one to three days) and sustained suppression of testosterone to castrate levels (serum testosterone level ≤50 ng/dL), thereby avoiding testosterone surge and flare of clinical symptoms.

Patients initiated with a GnRH receptor agonist regimen are on some occasions treated in combination with an anti-androgen during a limited period to avoid symptomatic flare associated with initial testosterone surge. Therefore, metastatic patients considered by the Investigator as requiring treatment with anti-androgen (e.g. bicalutamide 50 mg once a day) for a maximum period of up to 28 days in addition to leuprolide for symptomatic flare protection can be included and treated according to standard-of-care.

The most common side effects of leuprolide are hot flashes, pain (especially joint pain and back pain), injection site pain and fatigue (LUPRON Prescribing Information, 2014). Leuprolide may also cause impotence.

The risks of treatment with degarelix are likely to be associated with adverse reactions similar to those associated with other ADTs, such as hot flash/flushes, loss of libido, and impotence (Carter, 2014; FIRMAGON Prescribing Information, 2015).

Mild, transient elevated values of hepatic transaminases have been observed in healthy volunteers as well as prostate cancer patients treated with degarelix (Carter, 2014; FIRMAGON Prescribing Information, 2015). The hepatic changes observed to date have been transient increases in transaminases without concomitant increases in bilirubin and with no obvious correlation to dose,

duration of treatment, or degarelix plasma concentrations. Similar changes in hepatic transaminases were also seen with the active comparator, leuprolide, in the pivotal Phase 3 trial (FE 200486 CS21) (Clinical Trial Report FE 200486 CS21, 2008; Klotz, 2008). Blood samples for analysis of hepatic transaminase (alanine aminotransferase [ALT]) and serum bilirubin will be collected at baseline and at the End-of-Trial visit.

There is a risk of mild to moderate reactions at the injection site with degarelix. Injection site reaction adverse events were reported in 35% of patients treated with the 240/80 mg degarelix regimen in the CS21 trial (Clinical Trial Report FE 200486 CS21, 2008). The most commonly reported injection site reactions were pain (28%) and erythema (17%). These events occurred primarily after the starting dose of 240 mg degarelix.

Overall, more than 3,600 prostate cancer patients have been exposed to degarelix in clinical trials and the administration of degarelix has not revealed any significant safety concerns specific to degarelix. The cumulative exposure from post-marketing exposure is 275,253 patients (as of 17 August 2014) and no new important safety issues have been identified. It is considered that the benefit-risk profile for degarelix remains favorable. Patients included in the current trial will be monitored on a monthly basis during the entire course of the trial by central medical monitoring. An external Data and Safety Monitoring Board (DSMB) will on regular basis review safety data from the trial.

Adverse events and any CV-related signs or symptoms will be closely monitored during the trial to safeguard the health and well-being of the patients.

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

The secondary objectives are:

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) or 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 CV-related death in patients randomized to degarelix versus leuprolide

Prostate Cancer-Related Objectives

- To monitor testosterone levels at Days 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 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 (CT) 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 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 5 Levels 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

The exploratory objectives are:

- 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]

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 INVESTIGATIONAL PLAN

3.1 Overall Trial Design

3.1.1 Trial Design Diagram

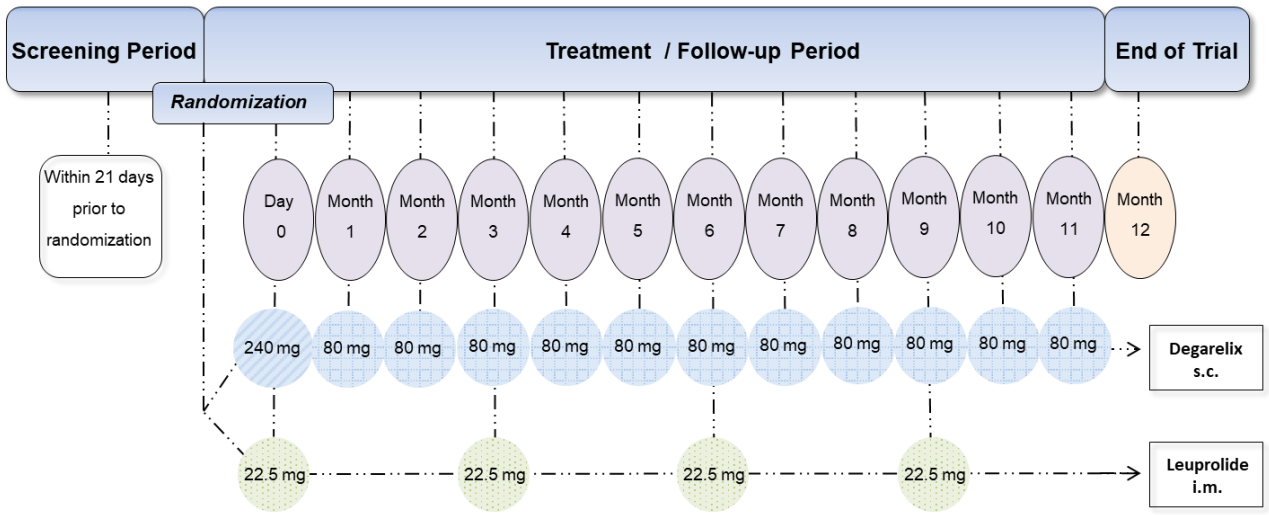

Figure 1 Trial Design Diagram

3.1.2 Overall Design and Control Methods

Trial Design

This is a multi-center, randomized, assessor-blind, controlled trial to compare the occurrence of 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 21 days prior to randomization for compliance with the inclusion and exclusion criteria. A trial design diagram is provided in Figure 1.

Patients will be randomized to one of the two treatments in a 1:1 ratio stratified by baseline age group and region, as detailed in Section 4.2.2. 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 assessors as described in Section 7.1.1.

Patients should be evaluated by a CV specialist to ensure that their CVD treatment is according to standard-of-care before trial entry. Cardiovascular disease information and source medical documents will be requested by the Investigator from the patient's CV specialist to evaluate and document CVD history for eligibility, using a Medical / CV History Request Form. A process will be implemented for the collection and review of supporting source data (with the involvement of the contract research organization [CRO] and Duke Clinical Research Institute [DCRI]) to ensure

the accuracy of patients' medical records documentation for the CVD-related inclusion criteria. The Investigator should ensure that pre-existing CVD and any CVD that may be diagnosed during the trial is managed by a CV specialist according to standard clinical practice. After randomization, the management of CVD and prostate cancer is intended to reflect standard-of-care.

If a patient experiences a CV event during the course of the trial, the Investigator will be encouraged to let the patient continue in the trial if this is not considered to constitute a safety concern. Patients who prematurely withdraw from the trial or from treatment with investigational medicinal product (IMP) will be followed-up for potential CV events and hospitalizations throughout the trial period as described in Section 4.4. If a patient is lost to follow-up, all attempts have to be made to obtain the vital and medical status of the patient at the planned end-of-trial for the patient.

Three committees with specific roles and responsibilities will be established for the trial; CEC Committee, DSMB, and Steering Committee. These committees are further specified in Section 3.4.

3.1.3 Trial Schedule

First patient first visit (FPFV) is estimated for Q1 2016 and last patient last visit (LPLV) is expected in Q2 2021. The expected duration of the total trial (from FPFV to LPLV) will be approximately 64 months; 52 months (1 month=1 calendar month) for recruitment and additional 12 months (1 month=28 days) for follow-up of last randomized patient.

3.2 Planned Number of Trial Sites and Patients

A 15-20% screening failure rate is expected based on previous experience in degarelix trials. Based on the expected screening failure rate and the sample size requirements of at least 876 patients treated in the trial (438 patients randomized to degarelix treatment and 438 patients randomized to leuprolide treatment), between 1,008 and 1,052 patients will be screened for participation in the trial. The sample size calculation is detailed in Section 9.1.

To achieve the requested number of patients within the given timelines, approximately 70 trial sites in the USA and Canada will be opened. Patient recruitment will be competitive between trial sites. At the time of the interim analysis, or if the recruitment rate is lower than expected, additional sites in other countries may be opened.

3.3 Interim Analysis

A single interim analysis is planned for the trial and will be performed by the statistician on the external DSMB established for the trial. The interim analysis will assess the hazard ratio, response rates of the adjudicated MACEs and reassess the sample size in the event that the stopping boundaries for futility are not crossed. The timing of the interim analysis is planned to correspond with the positive adjudication of the first 33 (50%) MACEs. The exact timing of the interim

analysis will depend on the accrual rate, as well as the event rate in the two treatment groups. The actual recruitment period and sample size may need to be adapted accordingly.

The interim analysis is further described in Section 9.9 and in the DSMB working procedure provided in a separate document.

3.4 Trial Committees

3.4.1 Clinical Events Classification Committee

An external independent CEC Committee will be established to provide an independent and blinded adjudication and classification of CV events throughout the trial. The CEC Committee will consist of 3 selected cardiology experts (including 1 chair), 1 neurology expert and 1 oncology expert not otherwise involved in the trial. In addition, 1 project leader and 1 coordinator at DCRI will support the CEC Committee activities. The complete adjudication process, including responsibilities and the composition of the CEC Committee, the schedule and format of the meetings, and the data to be evaluated are presented in a separate CEC charter.

The adjudicated MACEs will be used for the primary endpoint analysis (Section 7.1.1). Adjudicated MACE data will be transferred directly from the CEC Committee to the DSMB in order to keep those data blinded to the Sponsor.

3.4.2 Data and Safety Monitoring Board

The independent DSMB will consist of 1 chair, 1 voting independent statistician, 1 cardiologist and 1 urologist not otherwise involved in the trial. A non-voting statistician from the DSMB Independent Statistical Group (ISG) will attend DSMB meetings to present information and address questions related to the analyses. The major purpose of the DSMB is to periodically evaluate safety data throughout the trial period. An additional purpose of the DSMB is to perform a pre-planned unblinded interim analysis, assessing the treatment-related hazard ratio and event rates of the adjudicated MACEs. The responsibilities and the composition of the DSMB, the schedule and format of the meetings, the voting procedures, and the data to be evaluated are described in a separate charter document.

The DSMB will perform one pre-planned and unblinded interim analysis of the primary endpoint (Section 9.9) and will, based on pre-specified criteria, make recommendations to the Steering Committee whether to continue as is or, to modify (increase the sample size) or, to stop the trial due to futility according to predetermined criteria (outlined in the Statistical Analysis Plan [SAP] and the DSMB charter).

3.4.3 Steering Committee

The Steering Committee will consist of external experts (as a minimum a statistician, a cardiologist and a urologist) and a Sponsor representative who is not part of the trial team. The Steering Committee will be responsible for trial integrity and decisions related to the trial, such as protocol amendments and decisions based on interim recommendations by the DSMB as to whether the trial

is to be stopped, to be continued, or sample size is to be increased. The composition of the Steering Committee, the schedule and format of the meetings, and the voting procedures are presented in a separate Steering Committee charter.

3.5 Discussion of Overall Trial Design and Choice of Control Groups

3.5.1 Trial Design

The trial has a primary objective of assessing the effect of a GnRH receptor antagonist (degarelix) on the short-term CV risk as compared to a GnRH receptor agonist (leuprolide) in patients with prostate cancer and concomitant CVD. In addition, a number of non-CV-related secondary endpoints will be studied with the purpose to further investigate the potential differences in risk-benefit profile of degarelix versus GnRH receptor agonists.

In order to minimize the risk of imbalance between the treatment arms with respect to CVD prognostic risk factors the randomization will be stratified by baseline age group (<75 and ≥75 years of age) and region (North America and Other regions).

3.5.2 Selection of Endpoints

Androgen deprivation therapy has been reported to be associated with certain long-term metabolic effects, but also an increased risk of short-term major CV events. It has also been reported that history of CVD in prostate cancer patients is an increased risk factor for CV complications (Albertsen, 2014; Nguyen, 2014).

A pooled analysis of data from clinical trials has shown that patients, especially those with a history of CVD, may experience a significantly lower risk of CVD sequelae when treated with degarelix compared with a GnRH receptor agonist (Section 1.2). The primary objective is to assess the effect of a GnRH receptor antagonist (degarelix) on the short-term risk of the occurrence of MACEs (defined as 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. The CV endpoint definitions and methodology have been selected to conform to the Food and Drug Administration (FDA) guidance that is being developed on this topic (Hicks, 2015). The primary endpoint to compare CV risk between degarelix and leuprolide is defined as time from randomization to the first confirmed (adjudicated) occurrence of the MACE endpoint. Detailed descriptions of the methodology and CV endpoint definitions are given in a CEC charter provided in a separate document, as described in Section 3.4.1. The CV endpoint definitions are also provided in Appendix 1.

The secondary endpoints consist of CV-related endpoints including the individual components of the MACE endpoint as well as non-CV-related measures. Such secondary endpoints will be studied with the purpose to further investigate the potential differences in risk-benefit profile of degarelix versus a GnRH receptor agonist and include prostate cancer-related endpoints, health economics, and evaluation of safety. Endpoints relating to patient reported outcomes (PROs) are included to allow capturing directly the patients' perspective on the disease, and thus evaluating the impact of

its treatment on their emotional status and physical functioning. [redacted]

3.5.3 Blinding

The feasibility process conducted by the Sponsor has demonstrated that a true double-blind design would be difficult to implement (due to different doses and treatment regimen and different incidence of injection-site reactions) and would be unlikely to fully maintain blinding through the randomized treatment administration period. Specific firewalls will be implemented between the sites, the Sponsor and the MACE assessors to minimize risk of bias. An external CEC Committee (Section 3.4.1) will be established for the trial to provide an independent and blinded adjudication of CV events. The CEC Committee will have coordinators who will work closely with the Sponsor team for the surveillance and query processes to identify all potential CV events from the clinical and safety databases and work collaboratively to redact information regarding the open-label trial treatment information for each endpoint. This team would assist with generating queries specific to each endpoint reported and would be fire-walled from the external CEC Committee physician reviewers that process the completed event packets for physician adjudication to ensure complete blinding of the adjudication team. The CEC classification and adjudication process are detailed in a separate CEC charter.

3.5.4 Selection of Doses in the Trial

The regimen of a starting dose of 240 mg degarelix (40 mg/mL) followed by a maintenance dose of 80 mg degarelix (20 mg/mL) at monthly intervals (240/80 mg dose regimen) has been approved for the treatment of advanced prostate cancer by the medicines agencies in the European Union, the USA, and Canada.

The GnRH receptor agonist leuprolide (22.5 mg) will be administered intramuscularly (i.m.) every 3 months over the trial period as per current national label recommendations. Leuprolide and its 3-month depot formulation is selected as comparator, as being the most commonly used agent in this class of GnRH receptor agonists worldwide (*IMS MIDAS report: www.imshealth.com*). The Sponsor considers that the approved and standard-of-care dosing regimens specified above should be used in this trial.

3.5.5 Selection and Timing of Dose for Each Patient

Patients randomized to degarelix will receive a starting dose (240 mg degarelix) at Visit 2 (Month 0) followed by up to 11 maintenance doses (80 mg degarelix) at monthly (i.e. 28-day) intervals, according to the approved dosing regimen.

Patients randomized to leuprolide will receive one dose (22.5 mg leuprolide) every 3 months (i.e. 84 days), as per label recommendations, up to a total of 4 doses.

3.5.6 Selection of the Trial Population

Patients with hormone-dependent prostate cancer and pre-existing CVD considered at increased risk of adverse CV outcomes are to be included in the trial if the eligibility criteria in Section 4.1 are met. Patients must be treatment-naïve with regard to ADT at the time of randomization with the exception of neoadjuvant/adjuvant ADT for which the last injection of a depot formulation was at least 12 months prior to randomization (Section 4.3). It is considered that patients in whom therapy with either GnRH receptor antagonist or GnRH receptor agonist for at least one year is thought to be indicated according inclusion criterion No. 4 (Section 4.1.1) are consistent with and representing the approved indications of the IMP. The prostate cancer population is to reflect clinical practice in relation to ADT in patients with pre-existing severe CVD.

3.5.7 Withdrawal Criteria

In line with inclusion criterion No. 4 (Section 4.1.1), investigators and patients are encouraged to continue IMP treatment during the entire duration of the trial, unless clinical progression or medical status indicate otherwise at the discretion of the Investigator.

Specific withdrawal criteria and processes for IMP treatment and/or trial discontinuation are described in Section 4.4.

3.5.8 Follow-up Procedures

After the patient's last visit, the Investigator must follow-up on any adverse events that occurred during the trial and are classified as serious or as related to the IMP until it is resolved or until the medical condition of the patient is stable. All such relevant follow-up information must be reported to the Sponsor. If the event is a chronic condition, the Investigator and the Sponsor may agree that further follow-up is not required.

Following trial completion or premature IMP treatment and/or trial discontinuation, the Investigator may treat the patient according to normal practice.

Follow-up procedures in case of premature IMP treatment and/or trial discontinuation are described in Section 4.4.

4 SELECTION OF TRIAL POPULATION

4.1 Trial Population

4.1.1 Inclusion Criteria

Each patient must meet the following inclusion criteria before entry into the trial:

1. Signed informed consent obtained before any trial-related activity is performed.
2. Histologically confirmed adenocarcinoma of the prostate.
3. Clinical tumor staging (Tumor, Nodule and Metastasis [TNM]) available prior to treatment start; radiographic imaging (bone scan and/or CT scan and/or MRI) performed within 3 months prior to randomization. If no radiographic image is available at the time of screening, a bone scan should be performed.
4. Investigator judgment to initiate continued ADT with an intended treatment duration of 12 months or longer including any of the following disease categories:
    A. Patients with metastatic prostate cancer at the time of diagnosis.
    B. Patients with prostate cancer who develop metastases after local therapy.
    C. Patients with prostate cancer with very high-risk, high-risk or intermediate-risk disease with features of unfavourable prognosis who are going to be treated with definitive radiation therapy in combination with at least 12 months of neoadjuvant/adjuvant ADT.
    D. Patients with biochemical recurrence after local therapy who have a PSA doubling time <12 months.
    E. Patients previously treated with definitive local therapy (without ADT combination) who due to risk features such as positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA, will be treated with salvage radiation therapy in combination with neoadjuvant/adjuvant ADT that is planned for 12 months or longer.
    F. Patients with locally advanced prostate cancer who are not candidates (who are unsuited) for definitive therapy with surgery or radiation and will be treated with primary ADT.
5. Patients must be treatment-naïve with regard to ADT at time of randomization (with the exception of prior history of neoadjuvant/adjuvant ADT to definitive therapy for which the last administration, e.g., injection of a depot ADT formulation was at least 12 months prior to randomization).
6. Patients must have a screening serum testosterone level above the lower limit of normal range, defined as >150 ng/dL (5.2 nmol/L), apart from those who had prior neoadjuvant/adjuvant ADT (>12 months prior to randomization) where non-castrate range (>50 ng/dL or ≥1.73 nmol/L) should be applied.
7. Patients must have an Eastern Cooperative Oncology Group (ECOG) score of ≤2.

8. Pre-existing CVD (confirmed diagnosis prior to randomization) with **at least one** of the following criteria documented with applicable medical source documents:
    A. Prior myocardial infarction ≥30 days before randomization.
    B. Prior revascularization procedure ≥30 days before randomization, specified as any of the following:
        – Coronary artery stent placement or coronary artery balloon angioplasty
        – Coronary artery bypass graft surgery
        – Stent placement or balloon angioplasty to a carotid, iliac, femoral, or popliteal artery
        – Carotid endarterectomy surgery
        – Vascular bypass surgery of the iliac, femoral, or popliteal arteries
    C. Results from an angiogram or CT angiogram of the coronary, carotid, iliac, femoral, or popliteal arteries that documented at least one vascular stenosis ≥50% at any time point before randomization.
    D. Carotid ultrasound results that documented a vascular stenosis ≥50% at any time point before randomization.
    E. Ankle-brachial pressure index (ABPI) <0.9 at any time point before randomization.

4.1.2 Exclusion Criteria

A patient who meets one or more of the following exclusion criteria cannot be included in this trial:

1. Previous or current hormonal management of prostate cancer (surgical castration or other hormonal manipulation, including GnRH receptor agonists, GnRH receptor antagonists, anti-androgens, estrogens, megestrol acetate, ketoconazole, abiraterone and enzalutamide); except neoadjuvant/adjuvant ADT (in this case treatment has to be terminated at least 12 months prior to randomization).
2. Hypersensitivity towards any component of the IMPs or excipients.
3. Uncontrolled type 1 or type 2 diabetes mellitus (defined as hemoglobin A_{1c} [HbA_{1c}] >10%) at time of randomization.
4. Uncontrolled hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg) at time of randomization.
5. A history of congenital Long QT Syndrome or risk factors for Torsade de Pointes ventricular arrhythmias (e.g. heart failure, hypokalemia, concomitant medication known to cause QT prolongation).
6. Myocardial infarction within 30 days prior to randomization.
7. Stroke (hemorrhagic or ischemic) within 30 days prior to randomization.
8. Coronary, carotid, or peripheral artery revascularization within 30 days prior to randomization.

9. Planned or scheduled cardiac surgery or PCI procedure that is known at the time of randomization.
10. Other clinically significant disorder (other than prostate cancer and CVD) including, but not limited to, renal, hematological, gastrointestinal, endocrine, neurological, or psychiatric disease, and alcohol or drug abuse or any other condition, which may affect the patient's health or the outcome of the trial as judged by the Investigator.
11. Mental incapacity or language barrier precluding adequate understanding or co-operation.
12. Treatment with an investigational drug within the last month prior to randomization or longer if considered to possibly influence the outcome of the current trial or planned or concurrent participation in a clinical trial for any investigational drug or device.

4.2 Method of Assigning Patients to Treatment Groups

4.2.1 Recruitment

Approximately 70 trial sites in the USA and Canada will be opened. At the time of the interim analysis, or if the recruitment rate is lower than expected, additional sites in other countries may be opened. The participating patients will be recruited among the patients attending the clinics included in the trial. Advertisements may be used if approved by the Institutional Review Board (IRB)/Research Ethics Board (REB)/Independent Ethics Committee (IEC) and regulatory authorities, as applicable according to local regulations.

Each trial site will require potential participants to undergo a screening visit prior to randomization to a treatment group. Each patient who has given signed consent to participate in the trial will receive a unique screening number which must be entered in a screening log that must be maintained at each trial site. The screening number will be allocated sequentially in the order in which the patients are screened at the site, i.e. a patient must always be assigned to the lowest available screening number at each site. The results of each screening should be recorded in the screening log. The data for screened patients should also be entered in the electronic case report form (eCRF) with the reason for screening failure if the patient is not randomized to treatment. Under no circumstances will patients screened in the trial be permitted to be re-screened for a second time in this trial.

4.2.2 Randomization

Only patients who meet the eligibility criteria (Section 4.1) will be randomized to a treatment arm in this trial. The treatment arms will run in parallel.

Computer-generated randomization lists will be prepared centrally by the Sponsor's Department of Global Biometrics. Patients will be randomized to one of the two treatments in a 1:1 ratio stratified by baseline age group (<75 and ≥75 years of age) and region (North America and Other regions).

The patients will be randomized and allocated to a treatment through the eCRF and thereby receive a unique randomization number. The randomization must be performed at Visit 2 (Month 0).

4.3 Restrictions

4.3.1 Prior and Concomitant Therapies

Patients must be treatment-naïve with regard to ADT at time of randomization, except for neoadjuvant/adjuvant ADT given in combination with prostatectomy or radiotherapy with curative intent. This treatment should have been terminated at least 12 months prior to randomization.

Concomitant treatment with anti-androgens (e.g. bicalutamide 50 mg once a day) for a maximum period of up to 28 days is allowed in metastatic patients requiring initial symptomatic flare protection at the discretion of the Investigator. Other hormonal management of prostate cancer is not allowed prior to or during the trial (Section 4.1). However, if a patient develops signs of disease progression, e.g. increased clinical signs and symptoms or rising PSA, additional secondary therapy can be added at the discretion of the Investigator to treat the prostate cancer. Patients on secondary treatments will be handled as described in Section 4.3.2.

The Investigator will be encouraged to treat patients for their pre-existing CVD and any CVD that may be diagnosed during the trial according to standard-of-care. Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator.

Details of all concomitant medications, and other therapies including surgical procedures, e.g. revascularizations including the main reason for their prescription must be recorded in the medical source data and the eCRF for all eligible patients at the Screening visit. This information should include name of the drug, route of administration, indication, and duration of treatment. It has to be clearly stated if the medication is given to treat progression of the prostate cancer. Any changes (including new therapies) must be recorded at each subsequent trial visit.

4.3.2 Prohibited Therapy

Treatment with an investigational drug within the last month prior to randomization or longer is prohibited if considered to possibly influence the outcome of the trial.

The following concomitant medications are prohibited from randomization until the End-of-Trial:

- 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)
- Estrogens
- Megestrol acetate
- Ketoconazole
- Abiraterone
- Enzalutamide

In case any additional hormonal therapy has been initiated as a combination treatment with the IMP, this is considered a change of ADT regimen and the patient should be called in for an end-of-treatment visit and followed-up as described in Section 4.4.

4.3.3 Other Restrictions

Patients planning to father a child should not participate in this trial since the risks associated with sperm exposure to degarelix have not been evaluated.

4.4 Withdrawal Criteria

The patients have the right to withdraw from IMP treatment and/or the trial at any time for any reason without the need to justify their decision.

Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits/telephone contacts and from withdrawal of consent for non-patient contact follow-up, e.g., medical records checks. Therefore, when giving written consent for participation in the trial, patients will also be specifically asked to give written consent to safety follow-up procedures that will take place in case of withdrawal from IMP treatment, and/or in case a patient is lost to follow-up.

Patients should be informed that not giving consent, or requesting withdrawal of consent for safety follow-up, will jeopardize the public health value of the trial. Withdrawal of consent for safety follow-up should be accompanied by documentation of the reason for withdrawal.

Patients who withdraw from IMP treatment and/or the trial should be explicitly asked about the contribution of possible adverse events to their decision to withdraw consent, and any adverse event information elicited should be documented.

Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the trial site personnel should document and sign the reason for the patient's failure to withdraw consent in writing.

A patient who prematurely discontinues treatment with IMP, or receives prohibited medication (Section 4.3.2), should be called in for an end-of-treatment visit (Section 6.5) as soon as possible (within 30 days) after a decision of treatment discontinuation has been taken. The reason for premature IMP discontinuation should be recorded in the eCRF. The patient should then be contacted by telephone each month throughout the trial period for collection of follow-up information on hospitalizations and potential CV events, and concomitant medication. At the telephone follow-ups, information will be collected using the standardized questions regarding hospitalizations and/or ER visits that may have occurred since the last telephone follow-up as described in Section 8.2.3. In case the patient has experienced a potential CV event, related event documentation will need to be collected for evaluation by the CEC Committee. After 336 days of participation in the trial, the patient should be called in for an end-of-trial visit (Section 6.6).

In case a patient is lost to follow-up, despite every attempt (e.g., certified mail, telephone contact of patient or patient relatives) to get in contact, the vital and medical status of the patient should be investigated an additional last time at the end of the trial for that patient (i.e. 12 months after Visit 1), by accessing the patient's hospital records, or publicly available sources such as national registries, newspaper obituaries and social networking websites. Attempts may also be made to contact the patient or his relatives to ascertain this information. However, the patients have the right to withdraw their consent for collection of this information at any time, without the need to justify their decision.[a]

In case the patient has withdrawn his consent for participation in the trial, including any follow-up activities, no new data can be entered into the eCRF and data are recorded in the medical records only. Correction of previous data entries and/or entering of data related to visits/procedures done prior to but made available after withdrawal of consent (e.g. laboratory results) will be allowed unless the patient disapproves it.

The Investigator also has the right to withdraw patients from the trial or from treatment with IMP. Since an excessive rate of trial withdrawals or IMP treatment withdrawals can render the trial devoid of meaning, the unnecessary withdrawal of patients should be strictly avoided and all necessary measures should be taken to prevent withdrawals/discontinuations from IMP treatment. In case of the occurrence of any CV event, the Investigator will be encouraged to let the patient continue in the trial as per protocol if this is not considered to constitute a safety concern.

[a] ***Note:*** *In the UK, the following paragraph is applicable instead:*

In case a patient is lost to follow-up, despite every attempt (e.g., certified mail, telephone contact of patient or patient relatives) to get in contact, the vital and medical status of the patient should be investigated an additional last time at the end of the trial for that patient (i.e. 12 months after Visit 1), by accessing the patient's hospital records, or publicly available sources such as national registries and newspaper obituaries. Attempts may also be made to contact the patient or his relatives to ascertain this information. However, the patients have the right to withdraw their consent for collection of this information at any time, without the need to justify their decision.

Reasons for discontinuation from the trial or treatment with IMP include:

- Significant non-compliance to trial protocol, as judged by the Investigator and/or the Sponsor
- Other medical or safety reasons, as judged by the Investigator and/or the Sponsor

Patients discontinued from the trial will not be replaced.

5 TREATMENTS

5.1 Treatments Administered

A treatment flow chart is provided in Table 2.

Patients randomized to **degarelix** will receive:

Start of treatment (Month 0):

- A starting dose of 240 mg degarelix at a concentration of 40 mg/mL, administered as subcutaneous (s.c.) injections in the abdominal region via two equivalent injections of 120 mg each. The volume of each injection is 3.0 mL.

Month 1-11:

- Eleven (11) maintenance doses of 80 mg degarelix at a concentration of 20 mg/mL, administered at monthly (28-day) intervals as s.c. injections in the abdominal region via one injection of 80 mg, i.e. the volume of each injection is 4.0 mL.

Detailed administration guidelines for degarelix are given in the current national FIRMAGON label.

Patients randomized to **leuprolide** will receive:

Start of treatment (Month 0):

- One dose of 22.5 mg leuprolide, administered as a single i.m. injection according to the directions for use in the manufacturer's current national label. The volume of the injection is 1.5 mL.

Month 1-11:

- Three (3) doses of 22.5 mg leuprolide, administered as i.m. injections every 3 months (Month 3, 6, and 9) according to the directions for use in the manufacturer's current national label. The volume of each injection is 1.5 mL.

5.2 Characteristics and Source of Supply

All IMPs are provided by the Sponsor and will be handled according to the principles of Good Manufacturing Practice (GMP).

Degarelix

Degarelix is provided as commercially available kits for Starting Dose and Maintenance Dose:

- Starting Dose kit contains 2 sets of: 120 mg vial with powder for injection, prefilled syringe with 3 mL Sterile Water for Injection, vial adapter and administration needle (2 x 3.0 mL is withdrawn to deliver 240 mg degarelix at a concentration of 40 mg/mL)

- Maintenance Dose kit contains 1 vial with 80 mg powder for injection, prefilled syringe with 4.2 mL Sterile Water for Injection, vial adapter and administration needle (4.0 mL is withdrawn to deliver 80 mg degarelix at a concentration of 20 mg/mL)

Leuprolide

Leuprolide acetate is provided as commercially available kits containing one prefilled dual chamber syringe containing sterile lyophilized microspheres which, when mixed with diluent, become a suspension intended as an i.m. injection for 3-month administration (LUPRON DEPOT 22.5 mg).

5.3 Packaging and Labelling

Packaging and labelling of the IMPs will be performed under the responsibility of the Sponsor's IMP Department in accordance with GMP and national regulatory requirements.

Country-specific labels of the IMPs will be used. The labels will contain a self-adhesive tear-off portion to be affixed to the drug dispensing log maintained at the trial site. All products will be uniquely numbered with IMP number.

5.4 Conditions for Storage and Use

The Investigator will ensure that the IMP will be stored in appropriate conditions in a secure location with controlled access. The temperature in the storage compartment will be monitored regularly and the values shall be documented. Deviations in storage temperature must be reported without delay, and the IMP must not be used until further instructions from the Sponsor are received.

The products must be stored and handled in accordance with the commercial product label information.

5.5 Blinding / Unblinding

This is an assessor-blind trial. As described in Section 3.5.3, adjudication and classification of CV events for primary endpoint analysis will be performed by an external independent CEC Committee (Section 3.4.1) throughout the trial. Adjudicated MACE data for the pre-planned and unblinded interim analysis of the primary endpoint (Section 9.9) will be transferred directly from the CEC Committee to the DSMB (Section 3.4.2) in order to keep those data blinded to the Sponsor.

5.6 Treatment Compliance

5.6.1 Dispensing and Accountability

The IMPs will only be dispensed to patients who meet the eligibility criteria and are randomized to a treatment group in the trial. The IMP will be administered to the patient by authorized dedicated trial drug administrators at the trial sites.

The allocation of the IMP kits will be done through an Interactive Response Technology system. The administration of IMP should be documented at the site in the subject dispensing log. This is to include IMP kit number, batch numbers, expiration date and date and time of administration.

The dedicated monitor (a Sponsor representative) will verify the drug accountability during the trial. IMP carton kits (secondary packaging only) will be saved for drug accountability.

5.6.2 Assessment of Compliance

The IMP will be administered to the patient by authorized trial staff at the trial sites.

Overdoses and medication errors with and without clinical consequences must be reported as adverse events (Section 8.1). In presence of clinical reactions these must be reported as separate adverse events. In absence of clinical reactions this must be specified (Section 8.2.2).

5.7 Auxiliary Supplies

The Sponsor will provide the trial sites with needles, and other auxiliaries needed for preparation and administration of the IMP.

5.8 Return and Destruction of Medicinal Products and Auxiliary Supplies

All used IMP is to be destroyed at the trial site in accordance with local legislation after the drug accountability has been finalized and signed-off by the Investigator. If the IMP cannot be destroyed at the trial site it can be sent back to Warehouse/Sponsor after drug accountability has been finalized and signed-off by the Investigator.

All unused IMP will be returned for destruction, as instructed by the IMP Department at the Sponsor and in accordance with local requirements, after the drug accountability has been finalized.

6 TRIAL PROCEDURES

6.1 Trial Flow Chart

All patients must receive verbal and written information about the trial before entering the trial. Trial-related procedures must not be performed on a patient before the informed consent has been signed. The Investigator is obliged to keep logs of all screened and randomized patients. A flow chart of trial procedures and assessments per visit is provided in Table 1 and a treatment flow chart is presented in Table 2. All trial assessments are detailed in Section 7.

Table 1 Flow Chart of Assessments

	Screening	Treatment / Follow-up Period												End-of-Treatment [l]	End-of-Trial
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**		**14**
Month		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		**12**
Days from Visit 2	**Within 21 days prior to Visit 2**	**0**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**		**336**
Visit window (days)			**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		**±7**
Signed informed consent [a]	X														
Inclusion/exclusion criteria	X	X													
Demographics	X														
Medical history	X														
CVD history	X														
[redacted]		X												X	X
[redacted]		X												X	X
Height		X													
Physical examination	X													X	X
History/stage/histology of prostate cancer/ECOG [b]	X														
- Radiographic imaging [b, c]	X													X	X
Randomization		X													
Administration of IMP		*--- See separate treatment flow chart* (Table 2)---													
IPSS [d]		X			X			X			X			X	X
PRO [e]		X						X						X	X
Health economics [f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening	Treatment / Follow-up Period												End-of-Treatment [l]	End-of-Trial
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**		**14**
Month		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		**12**
Days from Visit 2	**Within 21 days prior to Visit 2**	**0**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**		**336**
Visit window (days)			**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		**±7**
12-lead ECG [g]		X	X					X						X	X
Vital signs (pulse and blood pressure) [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sampling: [g]															
- Testosterone [n]	X		X					X						X	X [m]
- Clinical chemistry	X	X	X					X						X	X
- Hematology	X	X												X	X
- Glycemic evaluation [h]	X	X												X	X
- Metabolic evaluation [i]		X												X	X
- PSA	X	X			X			X			X			X	X [m]
[redacted]		X													
[redacted]	X	X	X	X	X			X			X				X
Urine collection [g]	X	X												X	X
Drug accountability		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X														
Changes in concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events, including CV-related signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
End-of-Trial form															X

a) Signed informed consent must be obtained prior to any trial-related procedure.

b) Stage of prostate cancer should be based on clinical assessment and radiographic imaging (e.g. bone scan, MRI or CT performed as per standard clinical practice at the discretion of the Investigator) and should have been done within 3 months prior to randomization. If no radiographic image is available at the time of screening, a bone scan should be performed as part of the screening procedures. These data must be available for trial documentation before randomization.

c) The bone scan at the End-of-Trial visit (or End-of-Treatment visit) as part of the PFS endpoint follow-up can be performed up to 7 days before the actual visit.

d) The IPSS questionnaire should be completed by the patient before the PRO questionnaires DASI, CAQ and EQ-5D-5L.

e) PRO questionnaires: 1) DASI, 2) CAQ, and 3) EQ-5D-5L. The questionnaires should be completed in the given order.

f) Health economics: CV-related hospitalization events, CABG/PCI procedures and ER visit events.

g) ECG, vital signs, blood sampling, and urine collection must be performed prior to dosing. The results from the Screening visit must be available prior to randomization.

h) Glycemic evaluation at the Screening visit: HbA_{1c} in all patients (fasting not needed). Glycemic evaluation at Visit 2 and at the End-of-Trial visit: plasma glucose and serum insulin. The blood samples must be taken while the patient is in fasting state, i.e. minimum of 8 hours without caloric intake.

i) Metabolic evaluation: total cholesterol, HDL-cholesterol, low density lipoprotein LDL-cholesterol, triglycerides and uric acid. The blood samples must be taken while the patient is in fasting state, i.e. minimum of 8 hours without caloric intake.

[redacted]

[redacted]

l) Patients who prematurely discontinue treatment with IMP, or receive prohibited medication (Section 4.3.2), should be called in for an end-of-treatment visit as soon as possible (within 30 days) after a decision of treatment discontinuation has been taken. Following the End-of-Treatment visit, the patient will be followed-up as described in Section 4.4.

m) Blood sampling for analysis of testosterone and PSA should not be done in patients who have discontinued treatment with IMP and have performed an end-of-treatment visit.

n) Due to diurnal variations in testosterone level, patients with a screening serum testosterone level <150 ng/dL can be re-tested with laboratory results available prior to randomization, at the discretion of the Investigator.

Abbreviations: CABG, Coronary Artery By-Pass Grafting; CAQ, Cardiac Anxiety Questionnaire; CT, Computed Tomography; CV, Cardiovascular; DASI, Duke Activity Status Index; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, EuroQol Group 5 Dimensions 5 Levels Questionnaire; ER, emergency room; HbA_{1c}, hemoglobin A_{1c} (glycosylated hemoglobin); HDL, high density lipoprotein; [redacted] IMP, Investigational Medicinal Product; IPSS, International Prostate Symptom Score; LDL, low density lipoprotein; MRI, magnetic resonance imaging; [redacted] PCI, percutaneous coronary intervention; PFS, Progression-Free Survival; PRO Patient Reported Outcome; PSA, Prostate-Specific Antigen.

Table 2 Treatment Flow Chart

	Screening	Treatment/Follow-up Period												End-of-Trial
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Month		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Days from Visit 2	**Within 21 days prior to Visit 2**		**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**
Treatment window		**0**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Degarelix group Degarelix, s.c. [a]		2x 120 mg	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg	
Leuprolide group Leuprolide, i.m. [b]		22.5 mg			22.5 mg			22.5 mg			22.5 mg			

a) Degarelix starting dose, Visit 2: two s.c. depot injections, each containing 120 mg of degarelix (i.e. the starting dose will be 240 mg). The volume of each injection is 3.0 mL.
Degarelix maintenance doses, Visits 3-13: a single s.c. depot injection containing 80 mg of degarelix. The volume of each injection is 4.0 mL.

b) Leuprolide patients: one leuprolide 22.5 mg 3-month depot injected i.m. according to label recommendations, every 3 months throughout the trial. The volume of each injection is 1.5 mL.

Abbreviations: i.m., intramuscular; s.c., subcutaneous.

6.2 Visit 1 (Screening)

Patients will be screened within 21 days prior to randomization for compliance with the inclusion and exclusion criteria.

The following must take place at Visit 1:

- Signed and dated written informed consent, obtained prior to any trial-related procedures
- Allocation of a screening number
- Check of inclusion and exclusion criteria (those which are possible to check at screening)
- Demographics (age, ethnicity, race)
- Collection of the following data:
  - Medical history
  - CVD history using Medical / CV History Request Form
- Vital signs (pulse and blood pressure)
- Physical examination
- History/stage/histology of prostate cancer should be based on clinical assessment and radiographic imaging. Bone scan (MRI or CT may be performed as per standard clinical practice at the discretion of the Investigator) should be performed within 3 months prior to randomization
- Blood collection for central laboratory analysis of (*Note*: The result must be available prior to randomization.):
  - Testosterone (Due to diurnal variations in testosterone level, patients with a screening serum testosterone level <150 ng/dL may be re-tested prior to randomization, at the discretion of the Investigator.)
  - PSA
  - Clinical chemistry and hematology parameters
  - HbA_{1c}
- [redacted]
- Urinalysis (dipstick) (*Note*: The result must be available prior to randomization.)
- Recording of use of any concomitant medication (within the last 12 months prior to signed informed consent for participation in the trial)
- Adverse events, including CV-related signs

Patients considered eligible for the trial based on the inclusion and exclusion criteria assessed at this time point may proceed to the next visit (Visit 2).

6.3 Visit 2 (Month 0)

The following must take place prior to randomization:

- Ensure that the patient is still eligible for participation in the trial (including any changes in use of concomitant medications)
- Check those inclusion and exclusion criteria that were not possible to fully check during screening

Patients fulfilling all inclusion criteria and none of the exclusion criteria will proceed to randomization by an electronic system and thereby be allocated 1:1 (Section 4.2.2) to one of the two treatment groups.

The following must take place **after randomization, but before administration of the first dose of IMP (degarelix or leuprolide)**:

- IPSS
- PRO (DASI, CAQ and EQ-5D-5L)
- Health economics (CV-related hospitalization events, CABG/PCI procedures and ER visit events)
- Body measurements (body weight, waist and hip circumference, and height)
- [redacted]
- 12-lead electrocardiogram (ECG)
- Vital signs (pulse and blood pressure)
- Blood collection for central laboratory analysis of:
  - PSA
  - Clinical chemistry and hematology parameters
  - Glycemic and metabolic parameters (*Note*: The blood samples must be taken while the patient is in fasting state, i.e. minimum of 8 hours without caloric intake.)
  - [redacted]
- [redacted]
- Urinalysis (dipstick)

Once the above has been completed, the following must be performed by the drug administrator:

- Dispense and administer IMP (degarelix or leuprolide) according to randomization and treatment flow chart (Table 2)
- Dispense anti-androgen therapy to metastatic patients randomized to receive leuprolide in cases where this is prescribed for flare protection, at the discretion of the Investigator.

Finally, the following must be recorded before the patient leaves the clinic:

- Drug accountability
- Adverse events, including CV-related signs

6.4 Visit 3 (Month 1) to Visit 13 (Month 11)

6.4.1 Visit 3 (Month 1) to Visit 13 (Month 11) - All Visits

The procedures described in this section must take place at **all** visits (i.e. once monthly) from Visit 3 to Visit 13.

The following must take place **before administration of IMP**:

- Vital signs (pulse and blood pressure)
- Health economics (CV-related hospitalization events, CABG/PCI procedures and ER visit events)

Once the above has been completed, the following must be performed by the drug administrator:

- Dispense and administer IMP (degarelix or leuprolide) according to randomization and treatment flow chart (Table 2)

Finally, the following must be recorded before the patient leaves the clinic:

- Drug accountability
- Changes in use of concomitant medication
- Adverse events, including CV-related signs

6.4.2 Visit 3 (Month 1) and Visit 8 (Month 6)

- Blood collection (prior to dosing) for central laboratory analysis of:
  - Testosterone
  - Clinical chemistry parameters
- 12-lead ECG

6.4.3 Visit 3 (Month 1), Visit 4 (Month 2), Visit 5 (Month 3), Visit 8 (Month 6) and Visit 11 (Month 9)

[redacted]

6.4.4 Visit 5 (Month 3), Visit 8 (Month 6), and Visit 11 (Month 9)

The following additional procedure is recommended to be performed **before any other assessments** at Visits 5, 8 and 11:

- IPSS

The following additional procedure must be performed **before administration of IMP** at Visits 5, 8 and 11:

- Blood collection for central laboratory analysis of:
  - PSA

6.4.5 Visit 8 (Month 6)

The following additional procedures are recommended to be performed **before any other assessments** at Visit 8:

- PRO (DASI, CAQ and EQ-5D-5L)

6.5 End-of-Treatment Visit

Patients who prematurely discontinue treatment with IMP, or receive prohibited medication (Section 4.3.2), should be called in for an end-of-treatment visit as soon as possible (within 30 days) after a decision of treatment discontinuation has been taken.

The following must take place at the End-of-Treatment visit:

- IPSS
- PRO (DASI, CAQ and EQ-5D-5L)
- Health economics (CV-related hospitalization events, CABG/PCI procedures and ER visit events)
- 12-lead ECG
- Vital signs (pulse and blood pressure)
- Blood collection for central laboratory analysis of:
  - Testosterone
  - PSA
  - Clinical chemistry and hematology parameters
  - Glycemic and metabolic parameters *(Note*: The blood samples must be taken while the patient is in fasting state, i.e. minimum of 8 hours without caloric intake.)
- Urinalysis (dipstick)
- Body weight, waist and hip circumference
- [redacted]
- Physical examination
- Radiographic imaging (bone scan). (Imaging can be performed up to 7 days before the End-of-Treatment visit.)
- Drug accountability
- Recording of any change in use of concomitant medication

- Recording of adverse events, including CV-related signs
- Inform the patient about the planned follow-up and End-of-Trial visit

Following the End-of-Treatment visit, the patient will be followed-up as described in Section 4.4.

6.6 End-of-Trial Visit / Visit 14 (Month 12)

Patients should be called in for an end-of-trial visit after 336 days of participation in the trial.

The following must take place at the End-of-Trial visit:

- IPSS
- PRO (DASI, CAQ and EQ-5D-5L)
- Health economics (CV-related hospitalization events, CABG/PCI procedures and ER visit events)
- 12-lead ECG
- Vital signs (pulse and blood pressure)
- Blood collection for central laboratory analysis of:
  - Testosterone (*Note:* Not in patients who have discontinued treatment with IMP and have performed an end-of-treatment visit.)
  - PSA (*Note:* Not in patients who have discontinued treatment with IMP and have performed an end-of-treatment visit.)
  - Clinical chemistry and hematology parameters
  - Glycemic and metabolic parameters *(Note*: The blood samples must be taken while the patient is in fasting state, i.e. minimum of 8 hours without caloric intake.)
- [redacted]
- Urinalysis (dipstick)
- Body weight, waist and hip circumference
- [redacted]
- Physical examination
- Radiographic imaging (bone scan). (Imaging can be performed up to 7 days before the End-of-Trial visit.)
- Drug accountability
- Recording of any change in use of concomitant medication
- Recording of adverse events, including CV-related signs
- Completion of End-of-Trial form

6.7 Unscheduled Visits

The patient may be called in for additional unscheduled visits due to safety reason at the discretion of the Investigator or the Sponsor, unless the patient has withdrawn his consent. The patient may also contact the site due to safety reason for an unscheduled visit. The unscheduled visit may include additional collection of blood samples for safety reasons. The unscheduled visit may also include additional assessments deemed necessary by the Investigator such as laboratory samples, ECGs, or other procedures which were missed at a previous visit. All unscheduled visits should be described (including the reason for the visit) and documented in the medical/source record, and in the eCRF.

7 TRIAL ASSESSMENTS

7.1 Assessment Related to Primary Endpoint and Key Secondary Endpoints

7.1.1 Clinical Events Classification

Collection of CV-related adverse events will be performed from Visit 2 until the End-of-Trial visit as described in Section 8.2.3. An external CEC Committee will be established for the trial to provide an independent and blinded adjudication of CV events (see Section 3.4.1). A two-phase review process will be used and the adjudicated MACEs will be used for the primary endpoint analysis and the pre-planned interim analysis performed by the DSMB. The complete adjudication process and CV endpoint definitions are detailed in a CEC charter provided in a separate document. Cardiovascular endpoint definitions are also provided in Appendix 1.

Final analysis of CV endpoint data is solely the responsibility of the trial statistician and will thus be independent of the CEC Committee, the Investigators and site personnel as well as the patients.

7.2 Assessments Related to Other Secondary Endpoints

7.2.1 Prostate Cancer-Related Assessments

7.2.1.1 Testosterone

Blood samples for monitoring of serum testosterone levels will be collected at screening (Visit 1), at Visits 3 and 8 and at the End-of-Trial visit. The blood sampling must be performed prior to dosing. The analysis of testosterone will be performed by central laboratories.

Due to diurnal variations in serum testosterone level, patients with a screening serum testosterone level <150 ng/dL may be re-tested for eligibility prior to randomization, at the discretion of the Investigator.

Note: At the End-of-Trial visit, blood sampling for analysis of serum testosterone should not be performed in patients who have discontinued treatment with IMP and have performed an end-of-treatment visit where blood sampling for serum testosterone has been performed.

7.2.1.2 Progression-Free Survival

Prostate-Specific Antigen

Blood samples for analysis of PSA, as part of the PFS endpoint, will be collected at screening (Visit 1), at baseline (Visit 2), and every 3 months until the End-of-Trial visit (Visit 14). The blood sampling must be performed prior to dosing. The analysis of PSA will be performed by central laboratories.

Note: At the End-of-Trial visit, blood sampling for analysis of PSA should not be performed in patients who have discontinued treatment with IMP and have performed an end-of–treatment visit where blood sampling for PSA has been performed.

Radiographic Imaging

A bone scan follow-up will be performed in all patients at the End-of-Trial visit (or End-of-Treatment visit) as part of the PFS endpoint. The bone scan can be performed up to 7 days before the actual visit.

In addition, radiographic imaging (e.g. bone scan, MRI or CT performed as per standard clinical practice at the discretion of the Investigator) may be conducted in order to confirm suspected metastases as part of the PFS endpoint during the trial.

7.2.1.3 International Prostate Symptom Score

The most common symptom of prostate cancer is urinary obstruction with lower urinary tract symptoms (LUTS). Lower urinary tract symptoms will be measured with the IPSS Version 1 (standard version; IPSS-1) at baseline (Visit 2) and at Visits 5, 8 and 11 and at the End-of-Trial visit. At visits where PRO questionnaires also are to be completed the IPSS should be completed before the PRO questionnaires.

The IPSS is a tool commonly used to assess severity of LUTS, and also to monitor progress of the disease process once therapy has been initiated. The patient will complete a questionnaire containing seven questions regarding incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia. Each question will be assigned a score of 0 to 5. A score of "0" corresponds to a response of "not at all" for the first six symptoms and "none" for nocturia, and a score of 5 corresponds to a response of "almost always" for the first six symptoms and "5 times or more" for nocturia. The IPSS-1 includes an additional single question to assess a patient's QoL in relation to his urinary symptoms; the response to this question is analyzed separately and is not included in the total IPSS score.

7.2.2 Health Economics

7.2.2.1 Cardiovascular-Related Hospitalizations

Cardiovascular-related hospitalizations will be recorded at each visit from Visit 2 until the End-of-Trial visit.

7.2.2.2 Total Coronary Artery By-Pass Grafting and Percutaneous Coronary Intervention Procedures

Coronary artery by-pass grafting and PCI procedures will be recorded at each visit from Visit 2 until the End-of-Trial visit.

7.2.2.3 Emergency Room Visit Events

Emergency room visit events (that do not lead to hospitalizations) will be recorded at each visit from Visit 2 until the End-of-Trial visit.

7.2.3 Patient-Reported Outcomes

The PRO questionnaires are recommended to be completed before any other assessments are performed, by the patient in a quiet place without influence from trial personnel or accompanying family or friends. The trial personnel are not to help the patient choose an answer and must neither interpret nor rephrase questions which patients do not understand.

At visits where the IPSS (Section 7.2.1.3) is to be completed, the IPSS should be completed before the PRO questionnaires. The PRO questionnaires should then be completed in the following order: 1) DASI, 2) CAQ, and 3) EQ-5D-5L.

After completion of the questionnaires, the trial personnel will review the document for completeness only and enter the data into the eCRF. The patient should be given the opportunity to complete the questionnaire if this was not done in the first place, before leaving the site.

The questionnaires are validated for multinational use and will be provided in the local languages, as applicable.

7.2.3.1 Duke Activity Status Index and Cardiac Anxiety Questionnaire

The DASI and CAQ will be assessed at baseline (Visit 2), at Visit 8 and at the End-of-Trial visit.

The DASI is a self-administered instrument developed to measure functional capacity of CV patients. It contains 12 items referring to the present time assessing the ability to perform physical tasks in five domains: *personal care* (1 item), *ambulation* (4 items), *household tasks* (4 items), *sexual function* (1 item) and *recreation* (2 items). Each question is answered by one of four options: “yes with no difficulty” / “yes, but with some difficulty” / “no, I can’t do this” / “don’t do this for other reasons”. A global score is calculated with a higher score indicating a higher functional capacity.

The CAQ is a self-administered questionnaire developed to measure heart-focused anxiety in persons with or without heart disease. It contains 18 items referring to the present time assessing cardiac anxiety in three domains: *fear* (8 items), *avoidance* (5 items) and *attention* (5 items). Each question is assigned a score between 0 “never” to 4 “always”. A global score and scores per domain are computed with higher score indicating greater cardiac anxiety.

7.2.3.2 EQ-5D-5L

The EQ-5D-5L will be assessed at baseline (Visit 2), at Visit 8 and at the End-of-Trial visit.

EQ-5D-5L is a standardized measure of health status developed in order to provide a simple, generic measure of health for clinical and economic appraisal (*http://www.euroqol.org/home.html.*). EQ-5D-5L essentially consists of 2 systems - the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ VAS is an overall estimation of the present health status. An EQ-5D-5L health status estimation

may be converted to a single summary index by applying a formula that essentially attaches weights to each of the levels in each dimension. This formula is based on the valuation of EQ-5D-5L health status from general population samples in each country. Conversion from EQ-5D-5L into Quality Adjusted Life Year (QALY) units will create data for pharmacoeconomic evaluations of degarelix, as described in Section 9.6.3.13.

7.2.4 Safety Endpoints

7.2.4.1 Adverse Events

Adverse events will be recorded from Visit 1 until the End-of-Trial visit. Adverse events that occur before the administration of the first dose of IMP at Visit 2 will be regarded as pre-treatment adverse events. For each adverse event the following parameters are recorded on the Adverse Event Log: description of event, date and time of onset, intensity, causal relation to IMP, action taken to IMP, other actions taken, seriousness of the adverse event, date and time of outcome, and outcome. Definitions are provided in Section 8.1.

Data on suspected CV-related adverse events (except for pre-treatment events) will be delivered to the CEC Committee before the adjudication of MACE takes place (Sections 7.1.1 and 3.4.1). Potential CV-related adverse events will be closely followed.

In case of IMP treatment discontinuation, the patient should be followed for the entire duration of the trial for recording of adverse CV events (Section 4.4).

7.2.4.2 Vital Signs

Systolic and diastolic blood pressure (mmHg) and pulse (beats per minute) will be measured after resting for a minimum of 5 minutes in a sitting position at each visit throughout the trial. Assessments of vital signs must be performed prior to dosing if a dosing visit is scheduled.

At Visit 2, the systolic and diastolic blood pressure must not exceed 180 mmHg or 110 mmHg, respectively. If the initial reading exceeds these values, a second reading may be taken two or more hours later; the patient may be included (if all other inclusion criteria are met) in the trial if the second reading demonstrates a systolic blood pressure ≤180 mmHg and the diastolic blood pressure is ≤110 mmHg. If the blood pressure is brought to 180 mmHg systolic or less and 110 mmHg diastolic or less by antihypertensive treatment, the patient can become eligible.

Vital sign measurements outside normal ranges will be assessed as ‘abnormal, not clinically significant’, or ‘abnormal, clinically significant’ by the Investigator. ‘Abnormal, clinically significant’ measurements at the Screening visit will be recorded as medical history. ‘Abnormal, clinically significant’ changes in vital sign measurements will be reported as adverse events.

The process of evaluating potential CV-related vital signs is described in the CEC Charter in a separate document. Data on suspected CV-related vital signs will be delivered to the CEC Committee before the adjudication of MACE takes place (Sections 7.1.1 and 3.4.1). Potential CV-related vital sign results will be closely followed.

7.3 Other Assessments

7.3.1 Demographics

Demographic data will be collected at the Screening visit and will include date of birth, ethnicity and race.

7.3.2 Body Measurements

Body weight (without overcoat and shoes) will be measured at baseline (Visit 2) and at the End-of-Trial visit.

The patient's height (without shoes) will be measured at baseline (Visit 2).

[redacted]

Abnormal, clinically significant changes of body measurements will be reported as adverse events.

Data on potential suspected CVD-related body measurements will be delivered to the CEC Committee before the adjudication of MACE takes place (Sections 3.4.1 and 7.1.1).

7.3.3 Medical History Including Cardiovascular Disease History

Information on clinically significant previous and concomitant illnesses, other than prostate cancer, or any clinically significant signs or symptoms that are present before informed consent or findings from assessments and examinations done during screening will be recorded as medical history at the Screening visit. For planned procedures/hospitalizations during the trial, documentation should be completed at the time of the Screening visit.

The patients' CVD history will be collected by using a pre-specified Medical / CV History Request Form, which will be sent to the patients' CV specialist. The patient's eligibility will be based on the source documents received from the CV specialist.

7.3.4 Histology, Treatment History (or Previous Therapy), Stage of Prostate Cancer and Eastern Cooperative Oncology Group (ECOG) Score

The date of diagnosis of prostate cancer, stage of prostate cancer, and information on previous prostate cancer therapy will be recorded in the eCRF at the Screening visit. Moreover, the ECOG performance status will be assessed for eligibility.

Stage of the patient's prostate cancer prior to randomization will be based on clinical assessment and radiographic imaging (e.g. bone scan, MRI or CT performed as per standard clinical practice at

the discretion of the Investigator). Radiographic imaging should be performed within 3 months prior to randomization, and will be classified according to the TNM classification. In case no radiographic image is available prior to screening, a bone scan will be performed as part of the screening procedures. The TNM staging data must be available for trial documentation before randomization. The TNM stage both at the time of prostate cancer diagnosis and at the time of the Screening visit of this trial will be recorded.

For patients having undergone radical prostatectomy, pre-treatment TNM stage will be recorded.

Histology of the prostate cancer will be reported using Gleason grading. An appropriate Gleason grade for each of the two most predominant patterns will be recorded.

The ECOG performance status will be assessed according to the following scale (Oken, 1982):

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

[redacted]

7.3.6 Electrocardiogram

In this trial, 12-led ECG recordings will be performed at Visits 2, 3, 8, and at the End-of-Trial visit. The ECG must be performed after resting supine for 5 minutes and prior to dosing. The ECG measurements will include heartbeat, PR, QRS and QT intervals and T and U wave.

All ECG recordings will be evaluated according to normal clinical practice without any central ECG reading. The clinical significance of the ECG recording will be evaluated as ‘Normal’, ‘Abnormal, not clinically significant’, or ‘Abnormal, clinically significant’ by the Investigator or a cardiologist.

Additional unscheduled ECG recordings may be performed if deemed necessary by the Investigator. All unscheduled ECG recordings should be described (including the reason for the ECG recording) and documented in the medical/source record, and in the eCRF.

In case of any CV event that is to be submitted to the CEC Committee for MACE adjudication (Sections 7.1.1 and 3.4.1), any unscheduled ECG recording that has been performed should be sent to the CEC Committee and the baseline ECG is to be attached as a reference of pre-event status for comparison. For patients without CV event during the course of the trial, no analysis on ECG changes will be done.

Potential CV-related abnormal ECG results will be closely followed.

7.3.7 Physical Examination

Physical examinations will be performed by the Investigator or a delegated Sub-Investigator (MD, Medical Doctor; DO, Doctor of Osteopathic Medicine; PA, Physician Assistant; NP, Nurse Practitioner) and must not be delegated to any other trial site personnel. The same individual should preferably perform all physical examinations for a patient during the course of the trial.

A physical examination will be performed at the Screening visit and at the End-of-Trial visit for all patients. Abnormal, clinically significant findings at the Screening visit will be recorded as medical history. Abnormal, clinically significant changes in physical examination findings will be reported as adverse events.

7.3.8 Concomitant Medications / Therapies

Information on concomitant medication therapies, including surgical procedures, will be collected at each visit throughout the trial. Concomitant medications are defined as any medication taken by the patient at entry or during the trial, other than the IMPs (Section 5.1).

In case of IMP treatment discontinuation, the patient should be followed for the entire duration of the trial for recording of concomitant medications (Section 4.4).

7.3.9 Clinical Laboratory Variables

Blood samples for clinical laboratory analyses will be collected at the time points indicated in Table 1. The clinical laboratory variables to be evaluated are presented in Table 3. The analyses of clinical laboratory variables will be performed at a central laboratory using appropriate and validated methods.

Urine samples for urinalysis, will be collected at the Screening visit, at Visit 2 (prior to dosing), and at the End-of-Trial visit. The samples will be analyzed using a dipstick test at the clinic.

Blood samples for assessment of safety laboratory variables (clinical chemistry and hematology) will be collected at the Screening visit, at Visit 2 (prior to dosing) and at the End-of-Trial visit. In addition, blood samples for assessment of clinical chemistry will be collected at Visits 3 and 8 to allow for periodic safety monitoring for QT prolongation.

Blood samples for glycemic evaluations will be collected at the Screening visit, at Visit 2 and at the End-of-Trial visit. At the Screening visit, HbA_{1c} (glycosylated hemoglobin) will be tested in all

patients to rule out uncontrolled diabetes (HbA_{1c}>10%). Fasting plasma glucose and fasting serum insulin are to be measured at Visit 2 and at the End-of-Trial visit.

Blood samples for metabolic evaluations will be collected at Visit 2 and at the End-of-Trial visit.

The patients have to be in fasting state (minimum of 8 hours without caloric intake) prior to blood sampling for glycemic and metabolic evaluations at Visit 2 and at the End-of-Trial visit.

The total amount of blood, including blood samples for exploratory analyses (Section 7.3.10), planned to be collected from each patient during the course of the trial is approximately 200 mL. In case a patient is performing an unscheduled visit, an additional amount of blood might be taken (approximately 20 mL per visit, if applicable).

Table 3 Clinical Laboratory Variables

Glycaemia	Metabolism	Clinical Chemistry	Hematology	Urinalysis
Hemoglobin A_{1c} (HbA_{1c})	Total cholesterol	Albumin	Hematocrit	Blood
Fasting plasma glucose	High density lipoprotein (HDL)-cholesterol	Alkaline phosphatase (ALP)	Hemoglobin	Glucose
Fasting serum insulin	Low density lipoprotein (LDL)-cholesterol	Alanine aminotransferase (ALT)	Mean cell hemoglobin concentration (MCHC)	Ketones
	Triglycerides	Calcium	Mean cell volume (MCV)	Leucocytes
	Uric acid	Creatinine	Platelet count	pH
		Gamma-glutamyl transferase	Reticulocytes	Protein
		Potassium	Red blood cell (RBC) count	Nitrites
		Sodium	White blood cell (WBC) count with differential count: o Neutrophils o Eosinophils o Basophils o Lymphocytes o Monocytes	
		Total bilirubin		
		Urea/BUN (blood/urea/nitrogen)		

The Investigator will review the laboratory results and evaluate and document whether the results are normal or abnormal and whether abnormal results are non-clinically or clinically significant. The Laboratory Report will be signed and dated by the Investigator. 'Abnormal, clinically significant' laboratory values will be reported as adverse events.

In case of a CV event, data on suspected CV-related abnormal laboratory findings will be delivered to the CEC Committee before the adjudication of MACE takes place (Sections 3.4.1 and 7.1.1).

Potential CV-related laboratory results will be closely followed.

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

7.4 Handling, Storage and Destruction of Biological Samples

Blood samples will be handled in accordance with local regulations.

Central laboratories will be used for analysis of all blood samples for clinical laboratory analyses in this trial (Section 7.3.9). Sampling tubes, material for shipment of the samples, and a laboratory manual detailing all sample collection and shipment procedures will be provided and distributed to the trial sites by the central safety laboratory.

[redacted]

[redacted]

Urine samples will be analyzed at the clinic using a urine dipstick test (Section 7.3.9).

8 ADVERSE EVENTS

8.1 Adverse Event Definition

An adverse event is any untoward medical occurrence in a patient participating in a clinical trial. It includes:

- Any unfavorable and unintended sign, symptom or disease temporally associated with the use of the IMP, whether or not considered to be caused by the IMP.
- Adverse events commonly observed and adverse events anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality, vital sign or finding from physical examination assessed as clinically significant by the investigator (findings from assessments and examinations done during Screening are not adverse events, but are recorded as medical history)
- Accidental injuries, reasons for any change in medication (drug and/or dose), reasons for any medical, nursing or pharmacy consultation, or reasons for admission to hospital or surgical procedures.
- Overdoses and medication errors with and without clinical consequences.

8.2 Collection and Recording of Adverse Events

8.2.1 Collection of Adverse Events

The Investigator must monitor the condition of the patient throughout the trial from the time of obtaining informed consent until the last visit. Adverse events will be recorded from the time point of obtaining signed informed consent until the End-of-Trial visit. Any concomitant illnesses, other than prostate cancer, or any clinically significant signs or symptoms that are present at the Screening visit (Visit 1) will be recorded as medical history (Section 7.3.3). Adverse events that occur before administration of the first dose of IMP at Visit 2 will be regarded as pre-treatment adverse events.

The sources of adverse events cover:

- The patient's response to general questions about his health (a standard non-leading question such as "How have you been feeling since your last visit?" is asked at each visit)
- Symptoms spontaneously reported by the patient
- Investigations and examinations where the findings are assessed by the Investigator to be clinically significant changes or abnormalities
- Other information relating to the patient's health becoming known to the Investigator

8.2.2 Recording of Adverse Events

The Investigator must record all adverse events in the Adverse Event Log provided in each patient's eCRF with information about:

- Adverse event

- Date and time of onset
- Intensity
- Causal relationship to IMP
- Action taken to IMP
- Other action taken
- Date and time of outcome (time can be omitted, if applicable)
- Outcome
- Seriousness
- Relation to prostate cancer progression

Each of the items in the Adverse Event Log is described in detail in the following sections.

Adverse Event

Adverse events should be recorded as diagnoses, if available. If not, separate signs and symptoms should be recorded. One diagnosis/symptom should be entered per record.

The patient may contact the trial site for an unscheduled visit due to safety reasons. The patient may also be contacted by the site for an unscheduled visit in case of an important safety signal (e.g. an abnormal laboratory value), unless he has withdrawn his consent. Any such unscheduled visits will be captured in the eCRF under unscheduled visits. Unscheduled visits are detailed in Section 6.7.

If a patient suffers from the same adverse event more than once and the patient recovers in between the events, the adverse events should be recorded separately. If an adverse event changes in intensity, a worst-case approach should be used when recording the event, i.e. the highest intensity and the longest duration of the event should be applied.[b]

Note the following: A procedure is not an adverse event; the reason for conducting the procedure is. Hospitalization is not an adverse event; the reason for hospitalization is. Death is not an adverse event, but the cause of death is (an exception is sudden death of unknown cause, which is an adverse event).

[b] Exception: if an adverse event with onset before the first IMP administration (i.e. a pre-treatment adverse event) changes in intensity, this must be recorded as two separate events. The initial adverse event should be recorded with outcome "not yet recovered" and the date and time of outcome is when the intensity changed. The second adverse event should be recorded with date and time of onset when the intensity changed.

Date and Time of Onset

The date and time of onset is the date and time when the first sign(s) or symptom(s) were first noted. If the adverse event is an abnormal clinically significant laboratory test or outcome of an examination, the onset date is the date the sample was taken or the examination was performed.

Intensity / Common Terminology Criteria for Adverse Events Grading Scale

The Investigator must grade each adverse event according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (version 4.02). According to this guidance document all adverse events are rated on a 5-point scale corresponding to mild, moderate, severe, life-threatening or disabling and death. The guidance document will be provided to each trial site.

Each adverse event must be graded according to the specific criteria for grading as described in the CTCAE. For events not described in the CTCAE the following criteria will be used:

- Grade 1: Mild (minor; no specific medical intervention; asymptomatic laboratory findings only; marginal clinical relevance)
- Grade 2: Moderate (minimal intervention: local intervention; non-invasive intervention)
- Grade 3: Severe (significant symptoms, requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation)
- Grade 4: Life-threatening or disabling (complicated by acute, life-threatening metabolic or CV complications such as circulatory failure, hemorrhage, sepsis. Life-threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation)
- Grade 5: Death

Causal Relationship to IMP

The possibility of whether the IMP caused the adverse event must be classified as one of the following:

- Reasonable possibility:
  There is evidence or argument to suggest a causal relationship between the IMP and the adverse event. The adverse event may occur as part of the pharmacological action of the IMP or may be unpredictable in its occurrence.

  Examples:

  - Adverse events that are uncommon but are known to be strongly associated with IMP exposure.
  - Adverse events that are not commonly associated with IMP exposure, but the event occurs in association with other factors strongly suggesting causation, such as a strong temporal association or the event recurs on rechallenge.

- No reasonable possibility:
  There is no reasonable evidence or argument to suggest a causal relationship between the IMP and the adverse event.

  Examples:

  - Known consequences of the underlying disease or condition under investigation.
  - Adverse events common in the trial population, which are also anticipated to occur with some frequency during the course of the trial, regardless of IMP exposure.

Action Taken to IMP

The action taken to the IMP in response to an adverse event must be classified as one of the following:

- No change (medication schedule maintained or no action taken)
- Withdrawn
- Interrupted, e.g. in case of hospitalization

Other Action Taken

Adverse events requiring therapy must be treated with recognized standards of medical care to protect the health and well-being of the patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation.

If medication is administered to treat the adverse event, this medication should be entered in the Concomitant Medication Log.

Date and Time of Outcome

The date and time the patient recovered or died.

Outcome

The outcome of an adverse event must be classified as one of the following:

- Recovered (fully recovered or the condition has returned to the level observed at initiation of trial treatment)
- Recovered with sequelae (resulted in persistent or significant disability/incapacity)
- Recovering
- Not yet recovered
- Fatal

8.2.3 Cardiovascular-Related Adverse Events

The objective and scope of the present trial is to investigate the short-term risk of CV events in patients with pre-existing CVD. Thus, CV- related adverse events and any worsening in CV status will be recorded from Visit 2 until the End-of-Trial visit and will be captured separately in the eCRF.

At each monthly visit/contact with the patient, the Investigator must obtain information about:

- Admission to hospital or ER since last visit
- Death
- Admission for chest pain (ischemic) symptoms that could be an unstable angina or myocardial infarction event
- Admission for new neurological symptoms that could be a cerebrovascular (stroke) event
- Any drawn creatinine kinase (CK), creatine kinase-muscle brain (subunit) (CK-MBs) or troponin samples since last visit

The information obtained should be entered in the eCRF. In case pre-defined items on the eCRF checklist are answered affirmatively, a specific clinical endpoint form in the eCRF relating to each of the questions that were answered "yes", must be completed by the site personnel.

The following questions should be addressed directly to patients when reviewing this checklist at every monthly visit/contact:

Were you admitted to the hospital or visited the emergency department since your last visit/contact with us?

- If you were admitted to the hospital or visited the emergency department, was it due to symptoms such as chest pain (feeling of tightness, heavy pressure, squeezing or crushing pain), shortness of breath, nausea, fatigue, dizziness, or profuse sweating? These symptoms may have occurred at rest or during exercise.
- If you were admitted to the hospital or visited the emergency department, was it due to symptoms such as sudden onset of weakness or difficulty in coordinating muscles needed to speak (slurred speech), difficulty swallowing, visual impairment (you could not see well), or numbness or weakness of legs or arms (you could not properly lift or move your arms or legs)?
- If you were admitted to the hospital or visited the emergency department do you recall if the physician who treated you collected your blood to check if your heart muscle was damaged?

Data on potential CV-related adverse events will be delivered to the CEC Committee before the adjudication of MACEs take place (Sections 3.4.1 and 7.1.1). Potential CV-related adverse events will be closely followed.

In case of premature discontinuation of treatment with IMP or premature trial discontinuation, the patient should be followed for recording of CV events as described in Section 4.4.

8.2.4 Pregnancy and Pregnancy Outcome

In cases in which a foetus may have been exposed through transmission of the IMP via semen following paternal exposure, and the pregnancy results in an abnormal outcome (birth defect/congenital anomaly) this must be reported as a serious adverse event (SAE) to Global Pharmacovigilance (Section 8.3.2.1).

8.3 Serious Adverse Events

8.3.1 Serious Adverse Event Definition

Serious Adverse Events During the Trial

An event is defined an SAE if it:	Guidance
results in **death**	Any event resulting in a fatal outcome must be fully documented and reported, including deaths occurring within four weeks after the treatment ends and irrespective of the causal relationship to the IMP. The death of a patient enrolled in a trial is *per se* not an event, but an outcome.
is **life-threatening**	The term life-threatening refers to an adverse event in which the patient was at immediate risk of death at the time of the event. It does not refer to an event, which may have caused death if it were more severe.
requires in-patient **hospitalization** or prolongation of existing hospitalization	The term hospitalization means that the patient was admitted to hospital or that existing hospitalization was extended as a result of an event. Hospitalization describes a period of at least 24 hours. Over-night stay for observation, stay at ER or treatment on an out-patient basis do not constitute a hospitalization. However, medical judgment must always be exercised and when in doubt the case should be considered serious (i.e. if case fulfils the criterion for a medically important event). Hospitalizations for administrative or social purposes do not constitute an SAE. Hospital admissions and/or surgical operations planned before trial inclusion are not considered adverse events, if the illness or disease existed before the patient was enrolled in the trial, provided that the condition did not deteriorate during the trial.
results in persistent or significant **disability/incapacity**	Disability/incapacity means a substantial disruption of a person's ability to conduct normal life functions. In doubt, the decision should be left to medical judgment by the investigator.
is a **congenital anomaly/birth defect**	Congenital anomaly/birth defect observed in any offspring of the patient conceived during treatment with the IMP.
is an **important medical event**	Important medical events are events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of important medical events include adverse events that suggest a significant hazard, contraindication or precaution, occurrence of malignancy or development of drug dependency or drug abuse. Medical and scientific judgment should be exercised in deciding whether events qualify as medically important. Important medical events include any suspected transmission of an infectious agent via a medicinal product. Any organism virus or infectious particle (e.g. prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a medicinal product.

8.3.2 Collection, Recording and Reporting of Serious Adverse Events

8.3.2.1 Serious Adverse Event Reporting by the Investigator

All SAEs, except potential non-fatal MACEs (Section 8.3.2.2), must be reported **immediately** to the Global Pharmacovigilance Department at the Sponsor as soon as it becomes known to the Investigator and not later than within 24 hours of their knowledge of the occurrence of an SAE.

The Investigator is responsible for submitting the completed SAE Report Form with the fullest possible details **within 3 calendar days** of his/her knowledge of the SAE.

In this trial, the SAE form is part of the eCRF and will be submitted electronically.

eCRF information regarding demographics, adverse events, medical history and concomitant medication is **mandatory** for initial reports and for follow-up reports if any changes have been made since the initial report.

Additional information relevant to the SAE such as hospital records, results from investigations, e.g. laboratory parameters (that are not already uploaded in the eCRF), invasive procedures, scans and x-rays, and autopsy results can be faxed or scanned and e-mailed to the Global Pharmacovigilance Department at the Sponsor using the contact details below. In any case this information must be supplied by the Investigator upon request from the Sponsor. On any copies provided, such details such as patient's name, address, and hospital ID number should be concealed and instead patient number should be provided. The Investigator will supply the Sponsor and the IRB/REB/IEC with any additional requested information such as results of post-mortem examinations and hospital records.

In case the eCRF cannot be accessed and hence the SAE Report Form cannot be filled in within the eCRF system, a paper SAE Report Form should be used and sent to the Global Pharmacovigilance Department at the Sponsor using the contact details below. The information on the form must be transferred to the eCRF when the eCRF system has become accessible.

Contact Details for Serious Adverse Event Reporting

Global Pharmacovigilance, Ferring Pharmaceuticals A/S
Address: [redacted]
E-mail: [redacted]
Fax: [redacted]

8.3.2.2 Protocol Specific Exceptions to Serious Adverse Event Reporting

Specified CV-related endpoint events in the trial will be recorded in their respective appropriate modules of the eCRF. For these events, all necessary information, including whether or not the event meets the definition of "serious", will be collected in the eCRF. These events will NOT also require reporting as SAEs as described in Section 8.3.2.1. Specifically, the events covered in this exception are as follows:

- Myocardial infarction
- Stroke
- Unstable angina

All events leading to death should be reported as an SAE.

The DSMB will monitor suspected CV-related endpoint data and other safety data to ensure the safety of patients in the trial.

8.3.2.3 Expedited Reporting by the Sponsor

The Sponsor will report all adverse events that are **serious, unexpected and with a reasonable possible causality to the IMP** as judged by either the Investigator or the Sponsor to all investigators and to IRB/REB/IEC (responsibility Clinical Research & Development, Ferring Pharmaceuticals A/S) and to regulatory authorities (responsibility Global Pharmacovigilance, Ferring Pharmaceuticals A/S) within the stipulated timelines. The expectedness is assessed by the Sponsor according to the Prescribing Information of the IMPs.

In addition, adverse events identified by the Investigator or as potential CV-related signs will, regardless of causality, be provided by the Sponsor to the CEC Committee for adjudication (Sections 3.4.1 and 7.1.1).

Serious adverse events will be considered reportable regardless of whether or not the IMP was used in accordance with the provisions in the trial protocol and labelling.

8.4 Follow-up of Adverse Events and Serious Adverse Events

8.4.1 Follow-up of Adverse Events with Onset during the Trial

During the trial, the Investigator must follow-up on each adverse event until it is resolved or until the medical condition of the patient is stable.

After the patient's last visit, the Investigator must follow-up on adverse events that occurred during the trial and are classified as serious or as related to the IMP until it is resolved or until the medical condition of the patient is stable. All such relevant follow-up information must be reported to the Sponsor. If the event is a chronic condition, the Investigator and the Sponsor may agree that further follow-up is not required.

In case a patient is lost to follow-up, the vital and medical status of the patient at the end of the trial should be investigated as described in Section 4.4.

8.4.2 Collection of Serious Adverse Events with Onset after Last Trial Visit

If the Investigator becomes aware of an SAE after the patient's last trial visit, and he/she assesses the SAE to have a reasonable possible causality to the IMP, the case will have to be reported to the Sponsor, regardless how long after the end of the trial this takes place.

9 STATISTICAL METHODS

The Global Biometrics Department of the Sponsor will be responsible for the statistical analyses. All analyses will be detailed in a separate SAP.

9.1 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 a GnRH receptor agonist (leuprolide) in patients with prostate cancer and pre-existing CVD.

As suggested by a post-hoc analysis of degarelix safety data the 1-year event rates for a CV event or death due to any cause are 5.3% and 12.1% for degarelix and leuprolide, respectively, in the global patient population with prior CVD. 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 = [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 1-year event rates 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 [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 1-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.

9.1.1 Trial Design

One interim analysis (detailed in Section 9.9) is planned after 50% of the confirmed, adjudicated MACE endpoints has been collected. Due to the possibility of stopping the trial early for futility, an alternative hypothesis of a hazard ratio of 0.49 and 80% power, 66 events are required at final analysis, corresponding to 876 patients, in order to reject the null hypothesis of equal hazards at the two-sided 5% Type I error level. Note that the trial will not be stopped early due to an overwhelming treatment benefit.

9.1.2 Adjustments for Sample Size Re-Estimation

The conditional power for different sample size increases will be evaluated at the interim using ADDPLAN™ 6. In case of a sample size increase, the final test statistic is adjusted by using the normal inverse method. This 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 5.

Table 5 Sample Size Calculations (Number of Events Rounded Upwards)

Information Rate	Accept H_0			Reject H_0	α spent	Power Achieved	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

9.2 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.

The number of patients screened and randomized will be provided.

9.3 Protocol Deviations

Protocol deviations will be classified as either 'important' or 'non-important'. Important protocol deviations will be summarized by category and treatment group for the Full Analysis Set (FAS) to reflect general protocol adherence. No protocol deviations will lead to exclusion of data from the efficacy analyses. Individual important protocol deviations will be listed by patient.

9.4 Analysis Sets

9.4.1 Intention-to-Treat Analysis Set

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

9.4.2 Full Analysis Set

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

9.4.3 Safety Analysis Set

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

9.5 Trial Population

The trial population will be described for the FAS population.

9.5.1 Demographics and other Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics and medical history will be presented by treatment group for the FAS. In addition, summary of demographic and baseline

characteristics will be presented by trial site. [redacted]

Abnormal baseline ECG results (Section 7.3.6) will be listed by patient and trial site.

9.5.2 Medical History and Concomitant Medication

Medical history will be coded using MedDRA (version 17.1 or later) and tabulated by System Organ Class (SOC) and preferred term for the different analysis populations by treatment group. Concomitant medication will be coded using the Anatomical Therapeutic Chemical (ATC) classification system (World Health Organization [WHO] Drug Dictionary) and tabulated by the 1st level (Anatomic) and 2nd level (Therapeutic) for the same analyses sets.

9.6 Endpoint Assessments

9.6.1 General Considerations

The analysis of efficacy will be performed for the FAS. Unless otherwise specified, 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 trial or Day 336, whichever occurs first. In addition, all 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. P-values will be presented for all non-parametric tests, such as the log-rank test.

All regression models analyzing the time to MACE or the time to components of the MACE composite endpoint will be adjusted for the following CV risk factors measured at baseline: waist circumference, body mass index (BMI), [redacted] blood pressure, diabetes status, cholesterol and triglyceride levels. All semi-parametric and non-parametric models will be stratified by baseline age group and region.

9.6.2 Primary Endpoint

The primary endpoint, the time from randomization to the first confirmed occurrence of the composite MACE endpoint in the two treatment groups, will be analyzed based on the Kaplan-Meier estimator of the survival function and the log-rank test stratified for baseline age group and region.

The null hypothesis of equal hazard functions between the two treatment groups will be rejected if the test statistic exceeds the critical level for a two-sided hypothesis test with a Type I error level of 5%.

All CV events identified by the CEC Committee as adjudicated MACEs will be summarized by visit and treatment group and results of statistical analyses will be tabulated as appropriate.

In order to examine the robustness of the primary endpoint, the following sensitivity analyses will be performed:

- 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 the CV event unstable angina requiring hospitalization. Also, the endpoint will be analyzed as for the primary endpoint.

- Time to first confirmed occurrence of a MACE-related adverse event (myocardial infarction 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 the 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.

- Total occurrence of (adjudicated) myocardial infarction, stroke, and all-cause death

Total occurrence of myocardial infarction, stroke and all cause death is defined as the total number of events (myocardial infarction, 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.

- 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 in patients randomized in the trial will be used. Patients will be censored at lost to follow-up/withdrawal from the trial or Day 336, whichever occurs first.

9.6.3 Secondary Endpoints

If, and only 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

Other Secondary Analyses

The remaining secondary endpoints will be tested outside the scope of the hierarchy; without adjustment for multiplicity.

- 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
- Testosterone levels at Days 28, 168 and 336 in the degarelix and leuprolide treatment groups
- Time from randomization to failure in PFS
- Total number of CV-related hospitalization events 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 the treatment period
- Changes from baseline in PRO instruments will be analyzed longitudinally across the treatment period (IPSS and EQ-5D-5L) and cross-sectionally (DASI and CAQ)

Laboratory data, vital signs, and adverse events will be presented as appropriate.

Patients' functional capacity and heart-focused anxiety will be explored by describing DASI and CAQ scores at each visit and DASI and CAQ changes scores from baseline to each follow-up visit.

In addition, changes in scores over time will be explored and compared between patients treated with degarelix and patients treated by leuprolide using repeated measurement models.

Analyses of outcomes on health economic and PRO instruments will be detailed in the SAP.

All secondary endpoints will be summarized by visit and treatment group and results of statistical analyses will be tabulated as appropriate. Changes from baseline will be presented where appropriate.

9.6.3.1 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. Time, measured in days, from randomization to the 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 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.

9.6.3.2 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.

9.6.3.3 Time from Randomization to Confirmed (adjudicated) Cardiovascular-Related Death

Time from randomization to CV-related death is defined as the number of days from randomization to adjudicated CV-related death. Cause of death will be adjudicated by the external independent CEC Committee. Undetermined death will be presumed and analyzed as non-CV-related deaths on the secondary analysis. The time measured in days, from randomization to adjudicated CV-related death, will be analyzed as outlined in Section 9.6.3.2.

9.6.3.4 Time from Randomization to the First Confirmed (adjudicated) Unstable Angina Requiring Hospitalization

Time, measured in days, from randomization to first adjudicated hospitalization for unstable angina will be analyzed as the individual components of the MACE primary endpoint, as outlined in Section 9.6.3.2.

9.6.3.5 Time from Randomization to Death Due to Any Cause

Time from randomization to death due to any cause (overall survival) 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 CVD risk factors as appropriate and stratified by age group and region. The 95% confidence limits and associated p-values for the hazard ratio comparing treatment with degarelix to leuprolide will be presented.

9.6.3.6 Testosterone Levels at Days 28, 168 and 336 in the Degarelix and Leuprolide Treatment Groups

The proportion of patients with testosterone levels ≤0.5 ng/mL at each time point (Days 28, 168 and 336), as well as the proportion of patients with testosterone levels ≤0.5 ng/mL between Days 28 and 168 and Days 28 and 336, will be presented descriptively.

9.6.3.7 Time from Randomization to Failure in Progression-Free Survival

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

- 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 CT or MRI scan as confirmed by the Investigator.
- Introduction of additional therapy related to prostate cancer treatment including radiation, anti-androgens (except for initial flare protection) and second-line treatment.

- PSA failure 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.
- Death.

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. Time to PFS failure 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. 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.

9.6.3.8 International Prostate Symptom Score - Total and QoL Scores

The severity of LUTS will be investigated by their IPSS-1 score. IPSS-1 is a questionnaire containing seven questions regarding incomplete emptying, frequency, intermittency, urgency, weak stream, straining and nocturia. Each question is assigned a total score on a scale from 0 to 5. The total IPSS-1 score is then calculated as the summation over the responses for all 7 questions. The total IPSS-1 score will be transformed to a scale from 0 (lowest score) to 100 (highest score). The final question in the IPSS-1 questionnaire regarding QoL in relation to urinary symptoms will similarly be scaled from 0 to 100. The change from baseline to Month 3, 6, 9 and 12 in IPSS-1 total and QoL score will be compared between treatments longitudinally using repeated measures analysis of covariance (ANCOVA). Based on the ANCOVA model the two-sided 95% confidence limits of the adjusted treatment contrasts and associated p-values will be provided.

9.6.3.9 Total Number of Cardiovascular-Related Hospitalization Events Over the Duration of the Trial

The total number of CV-related hospitalization events 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 adjudicated CV-related hospitalizations, will be analyzed using a negative binomial model. The model will include a factor variable for treatment, the baseline count of CV-related hospitalizations as a covariate and the logarithm of the number of days of follow-up for each patient as an offset. The point estimate and 95% confidence limits of the rate ratio comparing the rate of CV-related hospitalizations among the degarelix and leuprolide treatment groups will be presented along with the associated p-value.

9.6.3.10 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 during follow-up will be analyzed using a negative binomial model as outlined in Section 9.6.3.9.

9.6.3.11 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 during follow-up for each patient will be analyzed using a negative binomial model as outlined in Section 9.6.3.9.

9.6.3.12 Duke Activity Status Index and Cardiac Anxiety Questionnaire Score

The DASI and CAQ will be assessed at baseline (Visit 2), Visit 8 and at the End-of-Trial visit. The change from baseline to Months 6 and 12 in DASI total score as well as CAQ total and domain scores will be compared between treatments both cross-sectionally using ANCOVA and longitudinally using repeated measures ANCOVA. Based on the ANCOVA models, the two-sided 95% confidence limits of the adjusted treatment contrasts and associated p-values will be provided.

9.6.3.13 Quality Adjusted Life Year

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.

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 ANCOVA model, where the QALY is the dependent variable with treatment as the comparison factor, respectively.

9.6.4 Exploratory Endpoints

The exploratory endpoint, time from the first non-fatal 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 GnRH receptor 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 recurrent events (Prentice, 1981) with a modification made based on the definition of the composite MACE endpoint. The model will be adjusted for the CVD risk factors measured at baseline, e.g. [redacted] blood pressure, triglyceride levels, BMI, waist circumference, diabetes status, and age. 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 the GnRH receptor agonist will be provided alongside the associated p-value. Significant results will be

interpreted cautiously, as randomization will not provide protection against imbalance of potential baseline CVD risk factors not adjusted for in the model, among the two groups at risk for a second MACE. The treatment effect of degarelix compared to leuprolide with respect to the rate of MACEs will be further explored via an Andersen-Gill model. 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]

9.7 Extent of Exposure and Treatment Compliance

Treatment compliance will be assessed on a by-patient basis by a listing of deviations from the doses to be administered per protocol and from the scheduled dosing intervals.

The cumulated dose administered to each patient will be determined and summarized descriptively.

9.8 Safety

9.8.1 General Considerations

Safety parameters will be evaluated for the safety analysis set (Section 9.4.3).

9.8.2 Adverse Events

Adverse events will be tabulated by SOC and preferred term using MedDRA version 17.1 or later. 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 presented. Adverse events will be

classified according to their intensity (using CTCAE version 4.02) and relationship to the IMP by the Investigator.

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.

Written narratives will be issued for all serious adverse events and adverse events leading to withdrawal. Missing values will be treated as missing, except for causality of adverse events to trial drug. If causality is missing, the adverse event will be regarded as being reasonably possibly related to IMP. Related adverse events (judged as being reasonably possibly related to trial drug) will be termed adverse drug reactions (ADRs).

An adverse event overview summary table will be prepared for the safety analysis set. It will display the number of patients reporting an adverse event, the percentage of patients (%) with an adverse event and the number of events reported for each treatment group. The following categories will be displayed:

- All adverse events
- Deaths
- SAEs
- Severe adverse events (CTCAE grade 3-5)
- Adverse events leading to withdrawal
- ADRs

Summary tables will be prepared for the incidence of treatment-emergent adverse events by MedDRA SOC (alphabetically) and preferred term (in decreasing frequency of occurrence). The tables will display the total number (N) of patients exposed, and the percentage of patients (%) reporting treatment-emergent adverse events. Summary tables will be prepared for:

- All adverse events
- Common adverse events (at least 5% of patients)
- Adverse events by causality (related/unrelated)
- Adverse events by intensity
- ADRs by intensity
- SAEs
- Adverse events leading to withdrawal

Supporting data listings will be provided for:

- Adverse events sorted by trial site/Investigator/patient number
- Adverse events sorted by MedDRA SOC and preferred term
- SAEs
- Adverse events leading to death
- Adverse events leading to withdrawal
- Adverse events adjudicated by the CEC Committee as MACE components

9.8.3 Vital Signs

Mean change and mean percentage (%) change from baseline at End-of-Trial will be presented for each vital sign variable. Also, the actual values and changes from baseline in vital signs will be tabulated by visit. Incidence of markedly abnormal changes in vital signs values will be summarized and results adjudicated by the CEC Committee as MACE components will be listed.

9.8.4 Other Safety Variables

9.8.4.1 Body Measurements

Mean change and mean percentage (%) change from baseline at End-of-Trial will be presented for body weight, BMI, waist circumference and waist-hip ratio. Incidence of markedly abnormal changes in body measurements will be summarized and results adjudicated by the CEC Committee as MACE components will be listed.

9.8.4.2 Physical Examination Findings

A listing of patients with abnormal physical examination findings will be presented by body system. For all patients in this listing, both baseline and End-of-Trial data will be included for comparison.

9.8.4.3 Safety Laboratory Variables

Mean change and mean percentage (%) change from baseline to the End-of-Trial will be presented for each laboratory variable.

Incidence of changes in laboratory values relative to normal reference ranges will be summarized.

Incidence of changes in urinalysis will be summarized.

Laboratory results adjudicated by the CEC Committee as MACE components will be listed.

9.8.4.4 Electrocardiogram

Abnormal ECG results (Section 7.3.6) will be listed by patient, visit and trial site.

9.9 Interim Analysis

One interim analysis is planned to be conducted based on the ITT analysis set when 50% of accumulated MACE information has been positively verified by the CEC Committee. Statistical information in this setting is proportional to the number of observed MACEs. The interim analysis is therefore planned to take place after the 33rd adjudicated MACE endpoint. The objective at the interim 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 DSMB may suggest to stop the trial due to futility. The futility bounds are non-binding. Due to the possibility of terminating the trial early based on futility the power is subsequently reduced, i.e. the risk of stopping a successful trial is inflated. To maintain 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 a close to zero spending of alpha at the interim analysis.

Based on the evaluation of the hazard ratio, the DSMB will have the option to recommend stopping the trial pre-maturely if any of the stopping boundaries are crossed. An O'Brien and Fleming type alpha spending function was used to compute the critical values for rejection, or acceptation of null hypothesis of equal hazards (Table 5).

The interim and primary analyses are planned to be performed at the specified information rate levels, while the actual recruitment may not be uniform. Therefore, the actual recruitment and follow-up periods may have to be adjusted such that the necessary amount of events are observed.

Increase of Sample Size

In case the stopping boundaries are not crossed, the required sample size will be reassessed, in order to achieve a conditional power of 80% at final data stage, given the current data and the trend of hazard rates (i.e. the maximum likelihood estimates). The reassessment of the sample size based on conditional power will be calculated using the inverse normal method (Wassmer, 2006), implemented in ADDPLAN version 6.0.8 or higher.

Details regarding the interim analysis are described separately in the SAP.

10 DATA HANDLING

10.1 Source Data and Source Documents

Source Data – International Conference on Harmonization Definition

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents - International Conference on Harmonization Definition

Source documents are defined as original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Electronic Source Data – FDA Guidance for Industry - Electronic Source Data in Clinical Investigations

If a process is used, by which the subject uses a Data Collection Instrument or an ePRO system, which has no prior written or electronic record, to directly record and transmit protocol data to a technology service provider database, the service provider database is the source.

Trial-specific Source Data Requirements – Sponsor

For each patient allocated to treatment, the Investigator will indicate in the hospital/medical source records that the patient participates in this trial and the date of obtaining the informed consent. The records should document data on the condition of the patient at the time the patient is enrolled in the trial to enable verification of eligibility. Signed and dated informed consent will be stored and archived according to local requirements. In addition, the following information, at the minimum, will also be recorded in the hospital/medical source records for each patient:

- Documentation of signed and dated Informed Consent
- Patient's name and date of birth
- Screening/treatment allocation number
- Trial identification
- Eligibility of participation in the trial (inclusion/exclusion)
- Body weight, height, waist and hip circumference
- Dosing of IMP - dose and administration date
- Documentation of endpoint questions addressed directly to the patient at each visit/contact

- Occurrence of any adverse events/SAEs (including description and duration)
- Medical history
- History, stage and histology of prostate cancer, and date of diagnosis
- History of pre-existing CVD
- Date of each visit
- Any concomitant therapy
- Status of the patient at the End-of-Trial
- Reason for IMP treatment discontinuation/withdrawal, if applicable

The following documents collected during the trial should be stored and archived together with the patient's hospital/medical records or in the Investigator File as agreed upon prior to the trial start at each trial site:

- Laboratory print-outs from central laboratory – evaluated, signed and dated by the Investigator
- ECG print-outs/reports – evaluated, signed and dated by the Investigator
- Patient dispensing logs of IMP
- Any trial assessment performed
- Any documentation obtained from other hospitals or medical centers regarding ER treatment or CV events

Examples of data that may be recorded on a paper source not necessarily being hospital/medical source records include the following:

- Evaluations of physical examinations
- Evaluations of vital signs
- Collection of laboratory samples
- Demographics
- [redacted]

10.2 Electronic Case Report Form

An eCRF system provided by an independent third-party CRO will be used for data capture. The system is validated and access at all levels to the system is granted/revoked following Sponsor and vendor procedures, in accordance with regulatory and system requirements.

Data entry into the eCRF system should be done in a reasonable time, preferably within 3 working days after each trial visit. The Investigator will approve/authorize the eCRF entries for each patient with an electronic signature which is equivalent to a handwritten signature.

The eCRF system and the database will be hosted at the independent third party CRO. After the trial database is declared clean and released to the statistician, a final copy of the database will be stored at the Sponsor. An identical copy of the database will be transferred to the DCRI for independent validation of the trial results to support scientific presentations and publications. The site investigators will receive a copy of the trial site's final and locked data (including audit trail, electronic signature and queries) as write-protected Portable Document Format (PDF) files produced by the independent third party CRO. The PDF-files will be stored on a CD and will be provided to the investigator before access to the eCRF is revoked.

Errors occurring in the eCRF will be corrected electronically. Such corrections/modifications will be automatically tracked by an audit trail detailing the date and time of the correction, the reason for the correction and the name of the person making the correction.

10.3 Use of Patient Reported Outcome Measures Instruments

An electronic PRO (ePRO) system provided by an independent third-party CRO will be used for collecting PRO measures.

The IPSS, DASI, CAQ, and EQ-5D-5L questionnaires will be collected using an electronic trial slate device to be completed by the patient.

In case of missing assessments, reasons should be recorded by trial personnel in the eCRF: questionnaire not given to the patient, patient refusal, lack of time from patient or functional limitation from patient to complete the questionnaire.

Handling of missing assessments and missing data will be detailed in the SAP.

10.4 Data Management

A data management plan will be created under the responsibility of the Global Biometrics department at the Sponsor. The data management plan will be issued before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation.

The data management plan will describe captured methods, who is authorized to enter the data, decisions about ownership of data, source data storage, which data will be transferred (including timing of transfers), the origin and destination of the data and who will have access to the data at all times.

10.5 Provision of Additional Information

On request, the Investigator will provide the Sponsor with additional data relating to the trial, duly anonymized and protected in accordance with applicable requirements.

11 MONITORING PROCEDURES

11.1 Periodic Monitoring

The monitor will review the electronic data capture (EDC) remotely on an ongoing basis throughout the trial, will conduct remote monitoring via phone calls with the site on a regular basis and will also visit the site periodically. The monitor will contact and visit the Investigator periodically to ensure adherence to the protocol, International Conference on Harmonization-Good Clinical Practice (ICH-GCP), standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy and verifiability of eCRF entries compared to source data, verification of drug accountability and compliance to safety reporting instructions.

The Investigator will permit the monitor direct access to all source data, including electronic medical records, and/or documents in order to facilitate data verification. The Investigator will co-operate with the monitor to ensure that any discrepancies that may be identified are resolved. The Investigator is expected to be able to meet the monitor during the on-site visits. When the first patient is randomized at the trial site a remote monitoring call visit will take place shortly afterwards to ensure adherence to the protocol.

11.2 Risk-Based and Adaptive Monitoring

Risk-based monitoring will be applied to this trial. The frequency of the on-site monitoring visits will be adapted depending on the risk level of the site and workload. Site risk is based on multiple factors including, but not limited to, the quantity of data generated at site, quality of source documents, unreported adverse events or SAEs and number of protocol deviations.

During on-site monitoring visits, the monitor will review medical records for suspected MACEs. The focus of on-site source review will be to detect any potential triggers including but not limited to:

- signs and symptoms reported by the patient
- changes in concomitant medication
- visits to specialists other than the treating investigator and the assessments performed
- the site's adherence to follow-up of patients that discontinued treatment prematurely, and if extensive efforts have been given to follow-up with patients that were lost to follow-up as described in Section 4.4

If an unreported adverse event is detected, additional source review will be performed for patient data not previously reviewed to minimize the risk of MACEs being missed.

The risk-based and adaptive monitoring, the source data verification process, and definition of key variables to be monitored are described in detail in the Monitoring Plan for the trial.

11.3 Centralized Monitoring

Centralized monitoring will be in place for the trial with focus on critical variables. Monitoring of the patterns of suspected MACE endpoint reporting (triggers) across the participating sites will be performed by a statistical team at DCRI. The objective will be to ensure as complete endpoint ascertainment as possible by identifying sites with anomalous patterns of reporting suspected MACEs. This activity will include the initial development of one or more statistical models, with possible modifications of the model(s) as the amount of available data increases. Trigger monitoring reports will be generated every other month throughout the trial. These reports will be carefully reviewed and applicable measures will be installed if required.

Additional approaches that will be implemented to ensure complete ascertainment of all potential MACEs are carefully delineated in the CEC Charter and include the implementation of structured questions that will trigger the reporting of potential MACE (when answered affirmatively) at every monthly patient visit, routine surveillance of the safety database to identify pre-selected MedDRA Preferred Terms related to the cardiovascular MACE endpoints studied to trigger the reporting of MACE endpoints (if not done already), and routine surveillance of the eCRF to query key data fields that could trigger the site to report a potential MACE. Details of this process are contained within Section 4.5 of the CEC Charter.

11.4 Audit and Inspection

The Investigator will make all the trial-related source data and records available at any time to quality assurance auditor mandated by the Sponsor, or to domestic/foreign regulatory inspectors or representatives from IRBs/REBs/IECs who may audit/inspect the trial.

The main purposes of an audit or inspection are to assess compliance with the trial protocol and the principles of ICH-GCP including the Declaration of Helsinki and all other relevant regulations.

The plan is to audit at least 10 (ten) percent of the sites each year of the trial duration. The first site audits will be conducted at the first sites entering patients into the trial. Selection of additional sites for audit will be based on an ongoing risk assessment, including, but not limited to, parameters such as recruitment rate and quality/compliance issues encountered during monitoring and/or auditing.

The patients must be informed by the Investigator and in the Patient Information/ Informed Consent Form that authorized personnel from the Sponsor and representatives from regulatory authorities and IRBs/REBs/IECs may wish to inspect their medical records. During audits/inspections the auditors/inspectors may copy relevant parts of the medical records. No personal identification apart from the screening/randomization number will appear on these copies.

The Investigator should notify the Sponsor without any delay of any inspection by a regulatory authority or IRB/REB/IEC.

11.5 Confidentiality of Patient Data

The Investigator will ensure that the confidentiality of the patients' data will be preserved. In the eCRF or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by an identification system, which consists of an assigned number in the trial. Documents that are not for submission to the Sponsor, e.g. the confidential patient identification code and the signed Informed Consent Documents, will be maintained by the Investigator in strict confidence.

12 CHANGES IN THE CONDUCT OF THE TRIAL

12.1 Protocol Amendments

Any change to this protocol will be documented in a protocol amendment, issued by the Sponsor, and agreed upon by the Co-Primary Investigators and the Sponsor prior to its implementation.

Amendments may be submitted for consideration to the approving IRBs/REBs/IECs and regulatory authorities, in accordance with local regulations. An approval by the IRBs/REBs/IECs is required for a substantial amendment, e.g., one which could affect the safety of the patients, or which entails a change to the scope/design of the trial.

Changes to the protocol to eliminate immediate hazard(s) to trial patients may be implemented prior to IRBs/REBs/IECs approval/favorable opinion.

12.2 Deviations from the Protocol

Deviations from the Protocol should not occur. If deviations from the protocol occur, the Investigator must inform the monitor, and the implications of the deviation must be reviewed and discussed. Any deviation must be documented, either as answer to a query in the eCRF, in a protocol deviation report or a combination of both. A log of protocol deviation reports will be maintained by the Sponsor. Protocol deviation reports and supporting documentation must be kept in the Investigator's File and in the Trial Master File.

12.3 Premature Trial Termination

Both the Investigator (with regard to his/her participation) and the Sponsor reserve the right to terminate the trial at any time. Should this become necessary, the procedures will be agreed upon after consultation between the two parties. In terminating the trial, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the best interests of the patients. Regulatory authorities and IRBs/REBs/IECs will be informed.

In addition, the Sponsor reserves the right to terminate the participation of individual trial sites. Conditions that may warrant termination include, but are not limited to, insufficient adherence to protocol requirements and failure to enter patients at an acceptable rate.

13 REPORTING AND PUBLICATION

13.1 Clinical Trial Report

The data and information collected during this trial will be reported in a clinical trial report prepared by the Sponsor and submitted for comments and signature to the signatory Investigators.

13.2 Confidentiality and Ownership of Trial Data

Any confidential information relating to the IMP or the trial, including any data and results from the trial will be the exclusive property of the Sponsor. The Investigator and any other persons involved in the trial will protect the confidentiality of this proprietary information belonging to the Sponsor.

13.3 Publications and Public Disclosure

13.3.1 Publications Committee and Policies

Prior to the end of the trial, a Publications Committee will be formed to include the trial Primary Investigators, other Steering Committee members, and Sponsor representatives. The Publication Committee will function as an independent body of scientific and medical experts acting to facilitate, encourage, and coordinate the complete and accurate presentation and publication of the trial results. The details regarding the processes that will govern the Publications Committee activities will be detailed in a separate Publications Committee Charter.

The Publication Committee will be responsible for the primary multicenter publication, and will review and approve other analyses suggested by Steering Committee members, Sponsor representatives, or other investigators at participating institutions. The Publication Committee will consider each analysis proposal with due regard for the scientific merit of the proposed publication with the aim of promoting the dissemination of scientific and medical knowledge.

Members of the Publication Committee, including Sponsor representatives, will read and constructively critique all abstracts and manuscripts prior to submission for presentation or publication. The Publication Committee will consider in good faith all comments provided by co-authors and Sponsor representatives during that review period.

The Sponsor will make all trial data available for independent statistical validation for the primary multicenter presentation and publication and for all other approved analyses.

All manuscripts approved by the Publication Committee will conform to the Uniform Requirements for Manuscript Submitted to Biomedical Journals, including, but not limited to the standards for authorship. Authorship will based on the International Committee of Medical Journal Editors (ICMJE) criteria (see current official version: *www.icmje.org/recommendations*).

13.3.2 Public Disclosure Policy

International Committee of Medical Journal Editors member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public, clinical trials registry. Thus, it is the responsibility of the Sponsor to register the trial in an appropriate public registry, i.e. *www.ClinicalTrials.gov,* which is a website maintained by the National Library of Medicine (NLM) at the U.S. NIH, and other public registries, as required.

14 ETHICAL AND REGULATORY ASPECTS

14.1 Institutional Review Board / Research Ethics Board / Independent Ethics Committee

An IRB/REB/IEC will review the protocol and any amendments and advertisements used for recruitment. The IRB/REB/IEC will review the Patient Information Sheet and the Informed Consent Form, their updates (if any), and any written materials given to the patients. A list of all IRBs/REBs/IECs to which the protocol has been submitted and the name of the committee chairmen will be included in the clinical trial report.

14.2 Regulatory Authorities Authorization / Approval / Notification

The regulatory permission to perform the trial will be obtained in accordance with applicable regulatory requirements. All ethical and regulatory approvals must be available before a patient is exposed to any trial-related procedure, including screening tests for eligibility.

14.3 End-of-Trial and End-of-Trial Notification

End-of-Trial is defined as the date the last patient performs the last visit in the trial.

At the end of the trial, the regulatory authorities and IRBs/REBs/IECs will be notified about the trial completion according to national requirements. In addition, a summary of the clinical trial report, e.g. the synopsis, will be provided when available and within one year of trial completion (defined as LPLV).

14.4 Ethical Conduct of the Trial

This trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013), in compliance with the approved protocol, ICH-GCP and applicable regulatory requirements.

14.5 Patient Information and Consent

The Investigator (or a medically qualified person delegated by the Investigator) will obtain a freely given written consent from each patient after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspects of the trial which are relevant to the patient's decision to participate. The trial patient must be given ample time to consider participation in the trial, before the consent is obtained. The Informed Consent Documents must be signed and dated by the patient and the Investigator who has provided information to the patient regarding the trial before the patient is exposed to any trial-related procedure, including screening tests for eligibility.

The Investigator (or the person delegated by the Investigator) will explain that the patient is completely free to refuse to enter the trial or to withdraw from it at any time, without any consequences for his further care and without the need to justify his decision.

Each patient will be asked to permit the Investigator to obtain CVD information and source medical documents from the patient's CV specialist to evaluate and document CVD history for eligibility. Each patient will also be asked to permit the Investigator to obtain medical documentation from other hospitals or medical centers regarding ER treatment or CV events for the patient during the trial period. In addition, each patient will be asked to permit the Investigator to obtain health-related follow-up information, e.g. by contacting the patient or his relatives, or access hospital records or publicly available sources such as national registries, newspaper obituaries and social networking websites, for a period of not more than 12 months after the patient has entered the trial.[c]

The patient will receive a copy of the Patient Information and his signed Informed Consent Form covering participation in the trial.

If new information becomes available that may be relevant to the trial patient's willingness to continue participation in the trial, a new Patient Information and Informed Consent Form will be forwarded to the IRBs/REBs/IECs (and regulatory authorities, if required). The trial patients will be informed about this new information and re-consent will be obtained.

Each patient will be informed that the Sponsor, monitor(s), quality assurance auditor(s) and other representative(s) mandated by the Sponsor, IRB/REB/IEC or regulatory authority inspector(s), in accordance with applicable regulatory requirements, may review his source records and data. Data protection will be handled in compliance with national/local regulations.

14.6 Patient Information Card

The patient will be provided with a Patient Information Card bearing the following information:

- That he is participating in a clinical trial
- That he is treated with GnRH receptor antagonist (degarelix) or GnRH receptor agonist (leuprolide)
- Name and phone number of the Investigator
- Trial code
- Name and address of the Sponsor (if required by local regulations)

The patient will be asked to return the Patient Information Card at the last trial visit, if applicable.

[c] ***Note:*** *In the UK, the following paragraph is applicable instead:*

Each patient will be asked to permit the Investigator to obtain CVD information and source medical documents from the patient's CV specialist to evaluate and document CVD history for eligibility. Each patient will also be asked to permit the Investigator to obtain medical documentation from other hospitals or medical centers regarding ER treatment or CV events for the patient during the trial period. In addition, each patient will be asked to permit the Investigator to obtain health-related follow-up information, e.g. by contacting the patient or his relatives, or access hospital records or publicly available sources such as national registries and newspaper obituaries, for a period of not more than 12 months after the patient has entered the trial.

Each patient's primary care physician and/or specialist will be notified of their participation in the trial by the Investigator, if the patient agrees.

14.7 Compliance Reference Documents

The Helsinki Declaration, the consolidated ICH-GCP, and other national laws in the countries where the trial takes place shall constitute the main reference guidelines for ethical and regulatory conduct.

15 LIABILITIES AND INSURANCE

15.1 ICH-GCP Responsibilities

The responsibilities of the Sponsor, the monitor and the Investigator are defined in the ICH-GCP consolidated guideline, and applicable regulatory requirements in the country where the trial takes place. The Investigator is responsible for adhering to the ICH-GCP responsibilities of investigators, for dispensing the IMP in accordance with the approved protocol or an approved amendment, and for its secure storage and safe handling throughout the trial.

15.2 Liabilities and Insurance

In case of any damage or injury occurring to a patient in association with the IMP or the participation in the trial, the Sponsor has contracted an insurance which covers the liability of the Sponsor, the Investigator and other persons involved in the trial in compliance with the laws in the countries involved.

16 ARCHIVING

16.1 Investigator File

The Investigator is responsible for maintaining all the records, which enable the conduct of the trial at the site to be fully understood, in compliance with ICH-GCP. The trial documentation including all the relevant correspondence should be kept by the Investigator for at least 15 years (or longer if so required by local law) after the completion or discontinuation of the trial, if no further instructions are given by the Sponsor.

The Investigator is responsible for the completion and maintenance of the confidential patient identification code which provides the sole link between named patient source records and anonymous eCRF and ePRO data. The Investigator must arrange for the retention of this Patient Identification Log and signed Informed Consent Documents for at least 15 years (or longer if so required by local law) after the completion or discontinuation of the trial.

No trial site document may be destroyed without prior written agreement between the Investigator and the Sponsor. Should the Investigator elect to assign the trial documents to another party, or move them to another location, the Sponsor must be notified. Documents may be transferred to the Global Quality Assurance of the Sponsor, for example if the Investigator retires and the documents no longer can be archived by the site. The Sponsor may also arrange for archiving of the Investigator File at an external archive.

16.2 Trial Master File

The Sponsor will archive the Trial Master File in accordance with ICH-GCP and applicable regulatory requirements.

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18 APPENDIX 1 Cardiovascular Endpoint Definitions

1 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.

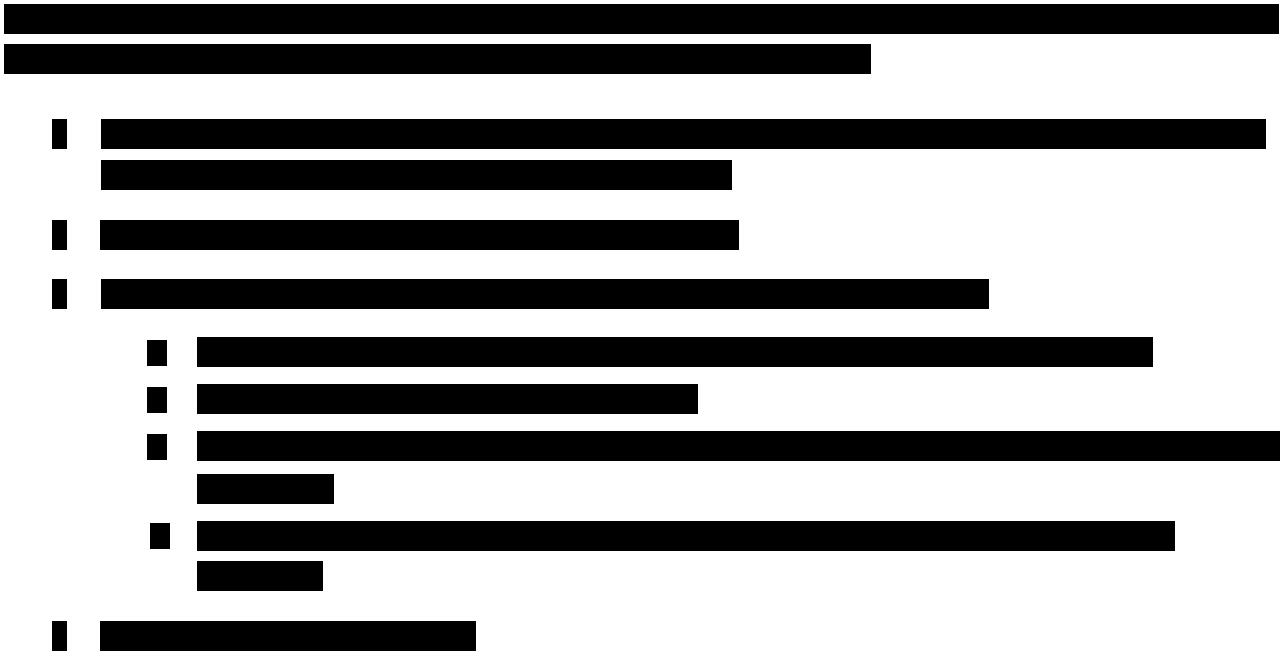
After CABG surgery, a myocardial infarction is defined as either:

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



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.