FERRING
PHARMACEUTICALS

Protocol

Title of study: A Prospective Observational Safety Study in Patients with Advanced Prostate Cancer Treated with Firmagon® (Degarelix) or a GnRH Agonist
NCT number: 01234350
Sponsor trial code: CS39
Date: 01 June 2010

Clinical Trial Protocol

A Prospective Observational Safety Study in Patients with Advanced Prostate Cancer Treated with Firmagon® (Degarelix) or a GnRH Agonist

FE 200486 CS39

Medicinal Product:	Firmagon® (degarelix powder and solvent for solution for injection)
Indication:	Advanced Prostate Cancer
Phase:	Observational Study
Name and Address of Sponsor:	Clinical R&D, Urology Ferring Pharmaceuticals A/S Kay Fiskers Plads 11 DK-2300 Copenhagen S Denmark Tel: +45 8833 8834

SYNOPSIS

TITLE OF STUDY

A Prospective Observational Safety Study in Patients with Advanced Prostate Cancer Treated with Firmagon® (Degarelix) or a GnRH Agonist

STUDY SITES

Approximately 250 sites in Europe

PLANNED STUDY PERIOD	**CLINICAL PHASE**
The first patient is estimated to enter the study approximately 6 months after the approval of the study protocol by the EMEA. The last patient will have completed the study approximately 7 years later, allowing a recruitment period of 2 years.	Observational Study

OBJECTIVES

Primary

The primary objective of this Observational study is to describe the risk of the following events in association with Firmagon treatment:

- Cardiovascular events
- Events related to decreased bone density, including new onset or progression of osteoporosis or osteopenia, and fractures
- New onset or exacerbation of glucose intolerance or type 2 diabetes mellitus
- Changes in hepatic enzyme levels

Secondary

The secondary objectives of this Observational study are to:

- Compare the relative risks of the adverse events of special interest in those patients treated with Firmagon and those treated with a gonadotropin releasing hormone (GnRH) agonist
- Identify any new potentially unrecognized adverse drug reactions (ADRs) by collecting adverse events (AEs) in this population
- Describe the long-term clinical evolution of prostate cancer (PCa) in patients treated with Firmagon
- Describe the all-cause mortality in patients treated with Firmagon

METHODOLOGY

Design

This Observational study is a multi-centre, long-term, prospective, observational cohort study to be conducted in multiple countries in the EU. Patients will enter the study after they begin treatment with androgen ablation therapy and will be followed for up to 5 years. There are no prescheduled visit regimens associated with the study. The visits in general should be part of routine clinical care and the information included into the study should also be part of the routine medical assessment. Baseline data will be collected at a routine outpatient visit, follow-up data will be collected at the time of routine office visits or by telephone interviews every 3 months for the first 2 years and every 6 months for the following 3 years.

All reasonable efforts and methods to minimize loss to follow-up will be undertaken to retain patients for the entire 5 years of observation, or until early discontinuation. This Observational study will enrol 1000 patients treated with Firmagon. In addition, a comparator group of 500 patients treated with any GnRH agonist will also be enrolled. The primary aim of the study is to better understand the safety profile of Firmagon; however, inclusion of a comparator arm will provide the ability to understand the results in the more general context of androgen ablation in PCa patients. Study enrolment will be monitored and enrolment of the control group will be locked once the target number of patients has been enrolled.

Assessments

<u>Baseline</u>

- Demographics (date of birth, race/ethnicity where allowed by local regulations)

- Height and weight (calculation of body mass index [BMI] will be based on these data)
- Waist circumference, if measured
- Medical history with a focus on PCa (including history, stage histology of PCa as well as previous cancer therapy), cardiovascular disease and bone fractures/osteoporosis/osteopenia as well as risk factors for cardiovascular disease and bone fractures/osteoporosis/osteopenia including smoking, alcohol consumption and level of physical activity, hyperlipidemia, hypertension, diabetes mellitus, hepatic disorders, renal disorders, and family history of cardiovascular disease, diabetes mellitus, and osteoporosis.
- All prescribed and over-the-counter concomitant medications, including bisphosphonates, lipid-lowering agents, anti-hypertensives, analgesics, short course anti-androgens, glucocorticoids, anti-angina drugs, and vitamin D/calcium supplementation
- Laboratories: hepatic enzymes, fasting blood glucose, testosterone, prostate-specific antigen (PSA), Dual energy X-ray absorptiometry (DEXA) bone scan, as available
- Prescribed androgen deprivation therapy (ADT)
- Prescribed anti-androgen therapy

Follow-up

- Assessments at 3-6 month intervals with specific questions related to cardiovascular, bone fracture, and diabetes mellitus, and other adverse events of special interest
- Adverse events throughout the 5-year period
- Laboratories: hepatic enzymes, fasting glucose, testosterone, PSA, DEXA bone scan, as available, estimated to be every 3 – 6 months

NUMBER OF PATIENTS

There will be 1,500 enrolled patients, of whom approximately 1,000 are to be treated with Firmagon and 500 with a GnRH agonist (ratio 2:1)

CRITERIA FOR INCLUSION / EXCLUSION

Inclusion Criteria

- Diagnosed with PCa and indicated for ADT
- Decision made to prescribe ADT (Firmagon or GnRH agonist) prior to enrolment
- Willing and able to provide written informed consent

Exclusion Criteria

Any patient meeting one or more of the following exclusion criteria may not be entered into the study:

- Participation in an interventional clinical study in which any treatment or follow-up is mandated
- Treatment with a GnRH receptor antagonist other than Firmagon
- Had previous or is currently under hormonal management of PCa, except for patients who have undergone therapy with a curative intention where neoadjuvant/adjuvant therapy allowed for maximum of 6 months. Treatment should be terminated at least 6 months prior to baseline.

STUDY TREATMENT

Patients will receive Firmagon or GnRH-agonist as prescription drugs. Medications will have been prescribed prior to screening at the discretion of the treating physician, and according to the approved Summary of Product Characteristics (SmPC) for Firmagon and the marketed GnRH agonists.

DURATION OF PARTICIPATION

Patients will be followed for five years, or until early discontinuation.

STATISTICAL METHODS

All demographic and disease baseline characteristics will be presented using descriptive statistics. All treatment-emergent AEs will be summarized. The mortality and respective incidence rates (number of adverse events per 100 person years) of, amongst others, serious cardiovascular events, bone fractures, onset of diabetes mellitus, will be estimated using the poisson model.

The following endpoints will be analysed:

1. Rate of adverse events of special interest
    a. Incidence rate of cardiovascular events
    b. Incidence rate of bone fracture, including osteoporotic/fragility fractures
    c. Incidence rate of new onset or worsening osteoporosis or osteopenia
    d. Incidence rate of new-onset diabetes mellitus
    e. Incidence rate of all-cause mortality

2. Occurrence of relevant laboratory value changes
    a. Changes in hepatic enzymes, fasting serum glucose, testosterone and PSA levels
    b. Incidence rate of glucose intolerance

Estimates will be accompanied with exact 95% confidence intervals as derived for both patients treated with Firmagon and those treated with a GnRH agonist. Poisson regression adjusting for key confounding factors (e.g., age, stage of disease) will be applied. In addition, the Cox Proportional Hazards model analysing time to first event data (with and without adjusting for potential confounding factors) will be performed. Respective cumulative incidence and their hazards, taking into account death and early study discontinuation as competing risks, will be estimated and compared between treatments. PCa status and any changes in selected laboratory results (e.g., PSA levels, DEXA bone scan) will be presented using descriptive summary statistics.

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LIST OF ABBREVIATIONS

ADT	Androgen Deprivation Therapy
AE	Adverse Event
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of Co-variance
ATC	Anatomical Therapeutic Chemical Classification System
BMD	Bone Mineral Density
BMI	Body Mass Index
CRF	Case Report Form
CRO	Contract Research Organization
e-CRF	Electronic Case Report Form
DEXA	Dual Energy X-ray Absorptiometry
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EMEA	The European Medicines Agency
EU	European Union
FDA	Food and Drug Administration, USA
FPFV	First Patient First Visit
GPP	Guidelines for Good Pharmacoepidemiology Practices
GnRH	Gonadotrophin Releasing Hormone
IEC	Independent Ethics Committee
LH	Luteinising Hormone
LLT	Lowest Level Term
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
PCa	Prostate Cancer
PSA	Prostate-Specific Antigen
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMQ	Standardised MedDRA Query
SmPC	Summary of Product Characteristics
SOC	System Organ Class

TNM	Tumour, Nodule, and Metastatic
TURP	Transurethral Resection of the Prostate

1 INTRODUCTION

1.1 Background

Prostate cancer (PCa) is the most common malignancy in men in Europe and the United States. In 2006, 345,900 new cases of PCa were diagnosed in Europe [1]. In the United States, the 2009 estimate for PCa cases is 192,280 new cases and 27,360 deaths [2]. PCa comprises 25% of new cancer cases in US males and about 20% of incident cancer cases in European males. Most patients diagnosed with PCa are over the age of 65, with the median age at diagnosis of 68 years [3].

Approximately 80% of PCa cases are diagnosed when the cancer is still confined to the primary site, with an additional 12% diagnosed when locally advanced and 4% when the cancer has already metastasized [4]. Treatment of localized PCa typically has a curative intent, and may include radical prostatectomy, radiotherapy, brachytherapy, high intensity focused ultrasound, cryotherapy, or hormone therapy. Watchful waiting or active surveillance may be employed in patients where the risks of treatment outweigh the benefits. Androgen deprivation therapy (ADT) is the most commonly used treatment for advanced PCa (tumour growth beyond the organ/organ capsule, infiltration of surrounding structures and lymph node metastases) and is primarily aimed at alleviating symptoms and slowing disease progression. PCa cells are initially hormone dependent and require receptor-mediated androgen stimulus for cell growth. Androgen deprivation leads to cell apoptosis and subsequent reduction in tumour burden. The majority of newly diagnosed PCa cases are initially hormone dependent and advanced PCa generally responds to hormone manipulation for approximately 12-18 months.

Androgen ablation by gonadotrophin releasing hormone (GnRH) agonists has been the mainstay of treatment for locally advanced and metastatic PCa for over 20 years. Although GnRH agonists are effective at achieving suppression of testosterone levels below castrate levels (< 50 ng/dl), they initially lead to an increase in luteinizing hormone (LH) levels and subsequent testosterone surge prior to down-regulation of the GnRH receptors of the pituitary gland. Patients with a large tumour burden may experience a clinical flare as a result of the testosterone surge, which could include worsening of bone pain, bladder outlet obstruction, spinal cord compression, and cardiovascular side effects [5]. Concomitant short course anti-androgen therapy is typically used to reduce the risk of clinical flare, but may result in additional burden of adverse drug reactions and higher cost. GnRH antagonists in contrast induce a rapid decline in testosterone and PSA levels without producing a testosterone surge or clinical flare [6].

Firmagon® (degarelix), a third generation GnRH antagonist, has been approved for the treatment of advanced PCa in the US (approved in 2008), Canada (approved in 2009), and in many countries in Europe (the first European country approved the drug in 2008). Firmagon represents a novel treatment option for men with advanced PCa who are at risk of complications due to the testosterone surge associated with GnRH agonist treatment.

A large body of scientific literature documents the adverse effects of induced hypogonadism, including vasomotor flushing, sexual dysfunction, fatigue, skeletal complications, and metabolic and cardiovascular complications [7] [8] [9]. ADT has been shown to decrease bone mineral density (BMD) [10] [11], and has been linked to increased risk of osteoporosis and fracture [12] [13] [14]. The metabolic changes brought on by androgen ablation are also well-studied, and include decreased insulin sensitivity, dyslipidemia, increased body mass index (BMI), and decreased lean body mass [15]. These metabolic changes may lead to an increased risk of type 2 diabetes mellitus and cardiovascular disease [16] [17] [18]. In a large cohort study of over 19,000 men treated continuously with ADT for at least 6 months, an increased risk of diabetes and fragility fractures was identified [19]. Most recently, a large linked register-based study in Swedish males with PCa presented evidence of an increased risk of myocardial infarction, cardiac arrhythmias, ischemic heart disease, and heart failure associated with endocrine treatment in PCa [20].

1.2 Study Rationale

An observational study has been chosen in order to obtain long-term safety data on Firmagon prescribed in the usual manner in accordance with the terms of the marketing authorisation. The population to be included in the study will be patients with hormone-dependent advanced PCa and there will be no restrictions concerning concomitant diseases and medications beyond patients which have previously been or are currently under hormonal management of PCa (refer to exclusion criteria). The target population for androgen ablation is inherently at increased risk of the events of interest, simply by virtue of advanced age (e.g., cardiovascular disease, stroke, fractures) and in some cases increasing background rates in the general population, such as with type 2 diabetes. Recent treatment guidelines, including guidelines of the European Association of Urology, recommend careful monitoring of all patients undergoing ADT for PCa, including Dual energy X-ray absorptiometry (DEXA) scans prior to beginning therapy [21]. The naturalistic study design provides the ability to better understand patient risk factors, real-world treatment patterns, and their association with the events of interest. It is also anticipated that the study could meaningfully contribute more broadly to the development of consistent clinical guidelines in the treatment of advanced PCa with androgen ablation.

In order to both meet the commitments required by the EMEA as part of marketing authorisation, and to better understand the risk factors and management patterns in patients treated with ADT, a large, long-term, prospective observational study in men treated with Firmagon and GnRH agonists will be conducted. The purpose of this Observational study is to study the long-term safety of Firmagon with a particular focus on new onset and exacerbation of fragility fractures, major alterations of glucose metabolism (glucose intolerance and type 2 diabetes), and cardiovascular events.

In accordance with the requirements for a non-interventional, observational study, the therapeutic strategy (Firmagon or GnRH therapy) is according to current practice (at the discretion of the physician). Subsequent to the physician's decision concerning treatment the patients will be enrolled into the study. A 2:1 allocation of patients to Firmagon is based on the main aim of the study, which is to assess the long-term safety of Firmagon. Although Firmagon works differently than GnRH agonists, specifically by binding reversibly to and blocking GnRH receptors on cells in the pituitary gland, the targeted end results of chronic hypogonadism, and its associated metabolic and cardiovascular risks, are expected to be comparable. However, the long-term effects of Firmagon on metabolism, fractures, diabetes, and cardiovascular outcomes have not been studied.

2 STUDY OBJECTIVES

2.1 Primary objectives

The primary objective of this Observational study is to describe the risk of the following events in association with Firmagon treatment:

- Cardiovascular events
- Events related to decreased bone density, including new onset or progression of osteoporosis or osteopenia, and fractures
- New onset or exacerbation of glucose intolerance or type 2 diabetes mellitus
- Changes in hepatic enzyme levels

2.2 Secondary objectives

The secondary objectives of this Observational study are to:

- Compare the relative risks of the adverse events of special interest (AESI) in those patients treated with Firmagon and those treated with a GnRH agonist
- Identify any new potentially unrecognized adverse drug reactions (ADRs) by collecting adverse events (AEs) in this population
- Describe the long-term clinical evolution of PCa in patients treated with Firmagon
- Describe the all-cause mortality in patients treated with Firmagon

3 METHODS

3.1 Study Design

This Observational study is a multi-centre, long-term, prospective, observational cohort study to be conducted in multiple countries in Europe. It constitutes a post-authorization safety study (PASS), to be conducted in compliance with Volume 9a of The Rules Governing Medicinal Products in the European Union (Guidelines on Pharmacovigilance of Medical Products for Human Use). Patients will enter the study after they begin treatment with androgen ablation therapy and will be followed for up to 5 years. Follow-up information will be collected every 3 months for the first 2 years and then every six months for the remaining 3 years or until patient discontinuation. There are no prescheduled visit regimens associated with the study. The visits in general should be part of routine clinical care and the information included into the study should also be part of the routine medical assessment. No procedures or examinations (e.g., physical exam, DEXA bone scan) are required as part of the study. Baseline data will be collected at a routine outpatient visit, follow-up data will be collected at the time of routine office visits or by telephone interviews at the approximate 3-month and 6-month time points.

All reasonable efforts and methods to minimize loss to follow-up will be undertaken to retain patients for the entire 5 years of observation, or until early discontinuation. This Observational study will enrol 1,000 patients treated with Firmagon. In addition, a comparator group of 500 patients treated with any GnRH agonist will also be enrolled. The primary aim of the study is to better understand the safety profile of Firmagon; however, inclusion of a comparator arm will provide the ability to understand the results in the more general context of androgen ablation and underlying PCa. Study enrolment will be monitored and enrolment of the control group will be locked once the target number of patients has been enrolled.

3.2 Study Treatment

The study will not provide or recommend any treatment, including androgen ablation therapy. All direction for medication usage and patient monitoring is solely at the discretion of the physician in accordance with their usual practice and consistent with the Summary of Product Characteristics (SmPC) of the prescribed medicinal product.

3.3 Limitations of Study Design

A non-randomised comparative observational study has several limitations. One of the most important limitations is that the decision concerning treatment (Firmagon or GnRH agonist) is according to the discretion of the treating physician. In order to address this potential allocation bias, there will be adjustments for baseline characteristics and PCa disease stage for the analyses.

Differences in the frequency of patient visits for patients treated with Firmagon and a GnRH agonist may be another limitation for this study. Firmagon will be administered subcutaneously at monthly intervals whereas most of the GnRH treatments will be administered at intervals of 3 months or longer. The differences in dosing schedules has been considered, and for this study, assessments with specific questions for adverse events of special interest (cardiovascular, fractures and diabetes) will be conducted at three month intervals for the first two years and six month intervals for the following three years. Telephone outreach will be used to attempt to minimise the differences in data collection due to the timing of patient visits.

3.4 External Advisory Board

An External Advisory Board will monitor the conduct of this Observational study and will specifically assess the ongoing results of the study. The Advisory Board will assess the period and cumulative Firmagon safety data at least twice a year for the first two years and annually for the duration of the study.

3.5 Interim Reporting

The progress of the study will be reported on an annual basis, including number of patients enrolled, duration of treatment, AEs, and the number of patients discontinued (including reasons for discontinuation). Incidence rates of cardiovascular, bone fractures and new-onset diabetes adverse events will also be presented.

4 SELECTION OF STUDY POPULATION

4.1 Study Population

A total of 1,500 patients will be recruited for participation, including approximately 1,000 patients treated with Firmagon and 500 patients treated with a GnRH agonist. The treating physician's decision concerning treatment will be made prior to the patient's inclusion in the study. An overall 2:1 distribution of patients to Firmagon: GnRH agonist will be pursued as the main aim of the study is to assess the long-term safety of Firmagon. Study enrolment will be monitored across sites, and once 500 patients are enrolled in the comparison arm, enrolment will be closed for that arm of the study.

The inclusion and exclusion criteria below are intended to be consistent with the indications and contraindications in the approved SmPCs for Firmagon and the marketed GnRH agonists.

4.1.1 Inclusion Criteria

The inclusion criteria for enrolment in the study are:

- Diagnosis with PCa and indicated for ADT
- Decision made to prescribe androgen ablation therapy (Firmagon or GnRH agonist) prior to enrolment
- Willing and able to provide written informed consent

4.1.2 Exclusion Criteria

Any patient meeting one or more of the following exclusion criteria may not be entered into the study:

- Participation in an interventional clinical study in which any treatment or follow-up is mandated
- Treatment with a GnRH receptor antagonist other than Firmagon
- Had previous or is currently under hormonal management of PCa, except for patients who have undergone therapy with a curative intention where neoadjuvant/adjuvant therapy allowed for max 6 months. Treatment should be terminated at least 6 months prior to screening visit.

4.2 Withdrawal Criteria

Patients may withdraw consent at any time. If a patient is withdrawn prior to completing the study follow-up period, any reason for withdrawal is to be documented in the database, if available. All information already collected as part of the study will be retained for analysis; however, no further efforts will be made to contact the patient guardian or record additional information in the study database.

4.3 Site Selection

Where possible a representative distribution of practice types with sufficient volume to meet sample size requirements will be selected. All patients seen at any of the study sites who meet the inclusion and none of the exclusion criteria detailed above may be included in the study. Sites will be required to maintain a patient enrolment log of eligible patients at each treatment centre. This log will document how patients came to be included or excluded from the study, in order to assess the representativeness of the study population. To the extent possible, consecutive eligible patients will be included.

4.4 Duration of Study

The first patient is estimated to enter the study approximately 6 months after the approval of the study protocol by the EMEA. The last patient will have completed the study approximately 7 years later. The goal will be to enrol all patients over a period of two years and to follow patients treated with Firmagon or a GnRH agonist for up to five years.

5 ASSESSMENTS

5.1 Schedule of Assessments

Patients will be enrolled after the initial decision has been made to treat with Firmagon or GnRH agonist. Data will be collected via a simple, streamlined electronic case report form (e-CRF) accessible by electronic data capture (EDC). Data will be collected at baseline and every 3 months (± 4 weeks) for the first 2 years, then every 6 months (± 6 weeks) for the remaining 3 years. Firmagon is dosed monthly, while GnRH agonists may be administered less frequently, therefore suggested data collection time points may not always coincide with treatment-related clinical visits. If necessary, telephone outreach may be used by sites to collect relevant data. Patients who discontinue ADT therapy will continue to be followed for safety outcomes in order to assess the long term safety associated with ADT.

A flowchart of recommended study assessments is provided in Table 1.

Table 1 Study Flow Chart

Visit	Baseline	Follow-up	
Time	0	0-2 years (3 months (± 4 weeks) between the visits)	2-5 years (6 months (± 6 weeks) between the visits)
Informed consent[a]	x		
Inclusion/exclusion criteria	x		
Demographics	x		
History/stage/histology of PCa	x	x	x
Body weight, height and waist circumference	x	x[b]	x[b]
Medical History	x		
Concomitant medications	x	x	x
Adverse events		x	x
ADT treatment		x	x
Fasting glucose, hepatic enzymes, DEXA bone scan	x[c]	x[c]	x[c]
PSA, testosterone	x[c]	x[c]	x[c]

a) Written informed consent must be obtained prior to any study related data collection
b) Height, weight, and waist circumference (waist circumference only if measured) should be collected at baseline and annually thereafter
c) At the discretion of the treating physician, estimated to be every 3 – 6 months.

5.1.1 Baseline

The following data, as recommended by current treatment guidelines [21], will be collected at baseline from the treating physician/medical record:

- Demographics (date of birth, race/ethnicity where allowed by local regulations)
- Height and weight (calculation of BMI will be based on these data)
- Waist circumference, if measured

- PCa status, including date of diagnosis, histology/(tumour, nodule, and metastatic) TNM classification, treatments to-date, Gleason score, evidence of extraprostatic extension, and Eastern Cooperative Oncology Group (ECOG) performance status (if available)
- Firmagon or GnRH agonist prescribed (dose and regimen, administered, start/stop date(s), complete/incomplete course, reason for change or discontinuation if applicable)
- Medical history
    - Relevant family history of PCa, cardiovascular disease, diabetes mellitus and osteoporosis
    - Cardiovascular disease
    - Bone fractures/osteoporosis/osteopenia
    - Cardiovascular disease and bone fractures/osteoporosis/osteopenia risk factors including positive family history, smoking [never; former/current (including pack years)], alcohol consumption [never; former (start and end date, average number of units per week); current (start date, average number of units per week], and level of physical activity (≥ 1 times/week, few times/month, rare/never), hyperlipidemia, hypertension
    - Diabetes mellitus or established glucose intolerance (e.g., fasting glucose 6.1-6.9 mmol/L)
    - Renal disorders
    - Hepatic disorders
    - Chronic respiratory disease (e.g., asthma, chronic obstructive pulmonary disease)
    - Allergies/Hypersensitivity
    - Other relevant medical history (specified)
- All prescribed and over-the-counter concomitant medications, including bisphosphonates, lipid-lowering agents, anti-hypertensives, analgesics, short course anti-androgens, glucocorticoids, anti-angina drugs, and vitamin D/calcium supplementation
- Most recent fasting glucose, hepatic enzyme levels (alanine aminotransferase, aspartate aminotransferase, bilirubin and alkaline phosphatase), pre-treatment PSA and testosterone levels, DEXA bone scan, as available.

5.1.2 Follow-up (up to 60 months post-enrolment)

No visits are mandated or prescheduled as a part of the study. Follow-up information will be collected at visits scheduled as a part of routine care, or will be collected via telephone interview if a visit does not occur during the data collection window. The data to be collected at the follow-up visits include adverse events and other clinical outcomes, including all outcomes of interest and new-onset co-morbidities, as follows:

- Survival status
- Cardiovascular events
    - Coronary artery disease, including myocardial infarction and unstable angina
    - Sudden cardiac death
    - Stroke
    - Cardiac failure

  - Cardiac arrhythmias
  - Embolic and thrombotic events
  - Cardiomyopathy
- Bone fractures
  - Any fracture, including osteoporotic/fragility fractures
  - New diagnosis of or worsening of existing osteoporosis or osteopenia
- Impaired glucose metabolism
  - New onset type 2 diabetes mellitus
  - Worsening of pre-existing diabetes mellitus
  - New onset of glucose intolerance (e.g., fasting glucose 6.1-6.9 mmol/L)
- Hepatic enzymes
  - Any change in hepatic enzyme levels (alanine aminotransferase, aspartate aminotransferase, bilirubin and alkaline phosphatase)
- Any changes in androgen ablation therapy
- Height, weight, and waist circumference (if measured) (annually)
- Selected laboratory results, if performed (fasting glucose, hepatic enzyme levels, PSA, testosterone)
- DEXA bone scan results (proximal femur and lumbar spine), if performed
- PCa status, including TNM classification, and need for additional therapeutic procedures related to PCa, such as Transurethral Resection of the Prostate (TURP)
- Updated concomitant medications

5.1.3 Study Discontinuation

At the time of follow-up completion, or early discontinuation, the date of study completion will be recorded. In the case of early discontinuation, the reason for discontinuation will also be recorded.

6 ADVERSE EVENTS

6.1 Adverse Events

6.1.1 Definitions

Adverse Event (AE)

An AE is any untoward medical occurrence in a patients participating in a clinical investigation who received a pharmaceutical product. An AE can be any unfavourable and unintended sign, symptom or disease temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product. This includes pre-existing medical condition that worsens in intensity during treatment. Overdose, abuse, misuse, inadvertent/erroneous administration, or medication error reports in association with a medicinal product should be recorded as an AE.

This definition also includes 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. It also includes AEs commonly observed and adverse events anticipated based on the pharmacological effect of the medicinal product.

Serious AEs (SAEs)

An SAE is any untoward medical occurrence or effect that at any dose that:

- Results in death[a]
- Is life-threatening[b]
- Requires in-patient hospitalisation or prolongation of existing hospitalisation[c]
- Results in persistent or significant disability/incapacity[d]

[a] The death of a patient enrolled in a study is per se not an event, but an outcome. Any event resulting in a fatal outcome must be fully documented and reported, including deaths occurring within 90 days after the treatment ends and irrespective of the causal relationship to the study drug.

[b] The term life threatening refers to an AE 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.

[c] The term hospitalisation means that the patient was admitted to hospital or that existing hospitalisation was extended as a result of an event. Hospitalisation describes a period of at least 24 hours. Over-night stay for observation, stay at emergency room or treatment on an out-patient basis do not constitute a hospitalisation. However, medical judgement must always be exercised and when in doubt the case should be considered serious (ie, if case fulfils the criterion for a medically important event). Hospitalisations for administrative or social purposes do not constitute an SAE. Hospital admissions and/or surgical operations planned before study inclusion are not considered adverse events, if the illness or disease existed before the patient was enrolled in the study, provided that the condition did not deteriorate during the study.

d 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 judgement by the treating physician.

- Is a congenital anomaly/birth defect[e]
- Is an important medical event[f]
- Any suspected transmission of an infectious agent via a medicinal product[g].

The seriousness criteria should not be confused with the intensity of the event.

Adverse Events of Special Interest (AESI)

A major objective of this observational study is to collect information on AESI, specifically cardiovascular events, bone fractures, and events associated with glucose intolerance. These events will be systematically collected at 3 or 6-month intervals with specific questions.

Cardiovascular events

- Coronary artery disease, including myocardial infarction
- Stroke
- Cardiac failure
- Cardiac arrhythmias
- Embolic and thrombotic events
- Cardiomyopathy

Bone fractures and associated conditions

- Any fracture, including osteoporotic fractures
- New diagnosis of or worsening of existing osteoporosis or osteopenia

Diabetes and glucose intolerance

- New onset diabetes mellitus or glucose intolerance
- Worsening of pre-existing diabetes mellitus

6.2 Collection and Recording of Adverse Events

AEs are to be collected from the time of obtaining Informed Consent until the end of follow-up, or until early discontinuation, as applicable.

e Congenital anomaly/birth defect observed in any offspring of the patient conceived during treatment with the medicinal product.

f Important medical events are events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of important medical events include AEs that suggest a significant hazard, contraindication or precaution, occurrence of malignancy or development of drug dependency or drug abuse. Medical and scientific judgement should be exercised in deciding whether events qualify as medically important.

g Any suspected transmission of an infectious agent via a medicinal product should be reported in an expedited manner. Any organism virus or infectious particle (eg, 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.

The treating physician must record all adverse events on the AE CRF module provided in each patient's e-CRF with information about:

- Event (verbatim)
- Date of onset [date when the first sign(s) or symptom(s) were first noted]
- Intensity [mild, moderate or severe]
- Causal relationship to medicinal product
- Action taken to medicinal product
- Other action taken
- Date of outcome
- Outcome [recovered, recovered with sequelae, not yet recovered, death]
- Serious [Yes/No]

Causal Relationship to Medicinal Product

The following 4-point scale will be used for rating the causal relationship of the AE to the medicinal product:

Unrelated: Clearly and incontrovertibly due only to extraneous causes, and does not meet criteria listed under unlikely, possible or probable.

Unlikely: Does not follow a reasonable temporal sequence from administration. May have been produced by the patient's clinical state, environmental factors or other therapies administered.

Possible: Follows a reasonable temporal sequence from administration. May have been produced by the patient's clinical state, environmental factors or other therapies administered.

Probable: Clear-cut temporal association with improvement on cessation of medicinal product or reduction in dose. Reappears upon re-challenge. Follows a known pattern of response to the medicinal product.

6.2.1 Collection and Recording of AEs and SAEs

All AEs should be recorded in the e-CRF with the information specified above. All SAEs reported during follow-up for patients exposed to at least one dose of Firmagon must also be reported to Ferring Global Pharmacovigilance for purposes of regulatory reporting. Site personnel will be responsible to complete and submit the appropriate Ferring SAE report form (available through the EDC system) and forward it to Ferring Global Pharmacovigilance within 24 hours of learning of the event (by either e-mail, phone call, or fax) according to contact details given in [Appendix 2]. Other information relevant to the SAEs such as hospital records, results from investigations e.g., laboratory parameters, invasive procedures, scans and x-rays, and autopsy results can be attached to the SAE Report Form and must in any case be supplied from the site upon request from the Sponsor.

The treating physician will supply the Sponsor and the Independent Ethics Committee (IEC) with any additional requested information such as results of post-mortem examinations and hospital records.

Post-Study Safety Collection

If a treating physician becomes aware of an SAE up until after 45 days after the patient either completes study follow-up, or discontinues early, the case should be reported to Ferring. Such reports will be considered for expedited reporting and managed as such by Ferring.

6.2.2 Regulatory Reporting Responsibilities

AEs/SAEs will be reported to local and regional health authorities by Ferring, when appropriate, in accordance with applicable local and regional regulations. The participating physicians are responsible for maintaining compliance with any applicable site-specific requirements related to the reporting of SAEs or other safety information to the local IEC that approved the study.

7 STATISTICAL METHODS

A detailed description of the analysis will be provided in the statistical analysis plan (SAP). This information may include details of missing and, if applicable, unused and spurious data. Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

All tabulations will be done by treatment arm. All individual patient data will be listed by domain. Additional sub-groups of interest, including by age strata, baseline Gleason score and TNM-stage, previous treatment for PCa and baseline risk factors will be used for stratification to the extent the volume of data allow.

7.1 Sample Size

In a pivotal one-year Phase 3 study (Ferring Clinical Study FE200486 CS21), a serious cardiovascular event rate for Firmagon of 5 per 100 patient-years was observed in the sub-group of patients with locally advanced or metastatic PCa. In the same study, in patients treated with the GnRH agonist (leuprolide) a serious cardiovascular event rate of 8 per 100 patient-years was observed. Based on SEER database in over 22,000 PCa patients treated with GnRH agonists the expected incidence rate is approximately 10 per 100 patient years [3]. In an observational study of 73,000 Medicare enrolees with locoregional PCa, Keating et al. [22] found incidence rates of 7.23, 1.29, and 1.35 respectively for coronary heart disease, sudden cardiac death, and myocardial infarction in patients treated with GnRH agonists. Keating et al additionally showed an incident rate for new onset diabetes of 2.90 in GnRH agonist treated patients.

In the CS21 study, a bone fracture rate of 0.6 per 100 patient years for patients treated with Firmagon vs. 2.2 per 100 patient years for patients treated with leuprolide was observed in the sub-group of patients with locally advanced or metastatic PCa. However, CS21 was a one-year study, and annual fracture rates increase with age and also with an increased number of doses of GnRH agonist [23]. Therefore, the incidence rates in a longer-term observational study are anticipated to be higher. Smith et al [24] report a fracture rate of 7.91 per 100 person-years in 3,779 men with PCa (all stages) who received GnRH agonist treatment during a 5-year observation period.

With the expected incidence rates for cardiovascular events, diabetes and fracture as indicated above, 1,000 patients on Firmagon, and 500 on GnRH agonist treatment for a 5-year follow-up study and assuming a dropout rate of 10% over the course of 5 years, and a uniform distribution for the time to dropout, the 95% confidence interval for estimating the incidence rates are listed in Table 2 below (please note that the confidence interval for the smaller comparator group will be wider). These confidence intervals show the precision for estimating the incidence rates if the observed incidence rates are the same as reported in literature. The width of the 95% confidence interval is also listed in the table. The calculation was performed in STATA 11 (College Station, TX).

Table 2 Incidence Rates for Cardiovascular Events and Fracture Reported in Literature, and the 95% Confidence Intervals the Study is Anticipated to Obtain Based on 1000 Patients on Firmagon and a Follow-up of 5 Years.

Event	Source	Incidence rate (per 100 patient years on Firmagon)	95% Confidence Interval	Width of the 95% confidence interval
Cardiovascular events	SEER data	10.00*	9.14, 10.91	1.77
	CS21	5.00	4.38, 5.68	1.30
Coronary heart disease	Keating et al.	7.23*	6.48, 8.02	1.54
Sudden cardiac death	Keating et al.	1.29*	.98, 1.66	0.68
Myocardial infarction	Keating et al.	1.35*	1.04, 1.74	0.70
Fractures	Smith et al.	7.91*	7.14, 8.74	1.60
	CS21	0.60	0.40, 0.87	0.47
New-onset diabetes	Keating et al.	2.90*	2.44, 3.45	1.01

*Incidence rate for GnRH agonist, assumed to be same with Firmagon

Based on the estimates and 95% Confidence Intervals widths described above, the planned sample size is considered sufficient to address the objectives of this Observational study, with reasonable precision.

7.2 Patient Disposition

All patients screened and enrolled into the study will be accounted for. All discontinuations after enrolment will be summarised by time of, and reason for, discontinuation.

7.3 Analysis Sets

The statistical analyses will be performed on the safety analysis set, which comprises all patients treated with at least one dose of medicinal product.

7.4 Study Population

7.4.1 Demographics and other Baseline Characteristics

Descriptive statistics of demographics, other baseline characteristics and medical history will be presented for all enrolled patients.

7.5 Safety Endpoint Assessments

The following endpoints will be analysed in the study:

1. Rate of adverse events of special interest (AESI)
    a. Incidence rate of cardiovascular events
    b. Incidence rate of bone fracture, including osteoporotic/fragility fractures
    c. Incidence rate of new onset or worsening osteoporosis or osteopenia
    d. Incidence rate of new-onset diabetes mellitus
    e. Incidence rate of all-cause mortality
2. Occurrence of relevant laboratory value changes
    a. Changes in hepatic enzymes, fasting serum glucose, testosterone and PSA levels
    b. Incidence rate of glucose intolerance

The AESI will be coded using MedDRA lowest level term (LLT). The following groups of AEs will be used for the analysis (with Standardised MedDRA queries [SMQs] in parenthesis, where applicable):

Cardiovascular Events

- Coronary artery disease, including myocardial infarction (Ischemic heart disease including sub-SMQ Myocardial infarction)
- Stroke (Central nervous system haemorrhages and cerebrovascular conditions including sub-SMQs hemorrhagic and ischemic cerebrovascular conditions, and conditions associated with CNS hemorrhages and cerebrovascular accidents)
- Cardiac Failure (Cardiac failure)
- Cardiac arrhythmias (Cardiac arrhythmias)
- Torsade de pointes/QT prolongation (Torsade de pointes/QT prolongation)
- Embolic and thrombotic events (sub-SMQs arterial, venous, and unspecified/mixed)
- Cardiomyopathy (Cardiomyopathy)

Fractures

- Any fracture, including osteoporotic fractures
- Osteoporosis/osteopenia

For fractures, relevant SMQ(s) will be used, if available. If no relevant SMQ(s) are available a predefined list of MedDRA preferred terms (PTs) to be used for the analysis will be included in the SAP.

Diabetes mellitus

- New onset diabetes mellitus
- Worsening of pre-existing diabetes mellitus

7.5.1 Statistical Analysis of Endpoints

The mortality rate and respective incidence rates (number of AEs per 100 person years) of, amongst others, cardiovascular events, bone fractures, onset of glucose intolerance or type 2 diabetes, will be estimated using the Poisson model. Estimates will be accompanied with 95% confidence for both treatment arms. Estimates and 95% confidence intervals of the incidence rate ratio (Firmagon to GnRH agonist) will be provided by applying Poisson regression model adjusting for key confounding factors (age and stage of disease amongst others).

In addition, the Cox Proportional Hazards model or Log Rank test will be applied to compare time to first adverse event (with and without adjusting for potential confounding factors) between treatment of Firmagon and GnRH agonist. Patients who are lost to follow-up before experiencing the adverse event of interest will be censored. This analysis will be repeated for each adverse event of interest.

Changes in fasting serum glucose, changes in serum hepatic enzymes, testosterone and PSA levels will presented by descriptive summary statistics for each treatment arm. The treatment groups will be compared using either an Analysis of Co-variance (ANCOVA; adjusting for baseline characteristics) or a non-parametric test (Wilcoxon test), as appropriate.

All other AEs will be summarized by treatment group, overall as well as in terms of intensity and relationship to study drug. Prior to preparing the summaries the adverse events will be coded using MedDRA obtaining both the system organ class and the PT.

7.6 Interim Reporting

The progress of the study will be reported on an annual basis, including number of patients enrolled, duration of treatment, AEs, and the number of patients discontinued (including reasons for discontinuation). Incidence rates of all cause mortality and AESIs will also be presented.

8 DATA HANDLING

8.1 Electronic e-CRF

In the study an e-CRF system provided by an independent third-party contract research organization (CRO) will be used for data capture. The system will be fully validated and access at all levels to the system is granted/revoked following sponsor and vendor procedures, in accordance with regulatory and system requirements. The e-CRF system and the database will be hosted at the independent third party CRO. After the study database is declared clean and is released to the statistician, a final copy of the database will be stored at the Sponsor.

The treating physician will approve/authorise the e-CRF entries for each patient with an electronic signature which is equivalent to a handwritten signature. Data should be entered into the system within three days after the patient has attended a visit or completed a telephone interview.

8.2 Data Management

A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation. The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the EDC system and followed up for resolution.

A complete, remapped, version of the database will be transferred to the Sponsor on an ongoing basis. Data validation will be performed the e-CRF system for all patients on an ongoing basis. Resolution of queries will be documented by study site personnel in the e-CRF.

8.3 Provision of Additional Information

On request, the treating physician will provide the Sponsor with additional data relating to the study, duly anonymised and protected in accordance with applicable requirements.

9 MONITORING PROCEDURES

9.1 Periodic Monitoring

Sites will be managed with e-mail and telephone contacts. In addition, a Monitor will visit 10% of the sites selected randomly at least once to ensure adherence to the Protocol and applicable regulatory requirements, maintenance of study-related source records, completeness, accuracy and verifiability of e-CRF entries compared to source data. More sites might be visited if deemed needed. The treating physician will permit the Monitor direct access to all source data and/or documents in order to facilitate source data verification. This includes electronic medical records that also must be accessible for the Monitor for source data verification. The treating physician will co-operate with the Monitor to ensure that any discrepancies that may be identified are resolved. The treating physician is expected to be able to meet the Monitor during these visits.

9.2 Confidentiality of Patient Data

The treating physician will ensure that the confidentiality of the patients' data will be preserved. In the e-CRF 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 study. Documents that are not for submission to the Sponsor, e.g. the confidential patient identification code and the signed Informed Consent forms, will be maintained by the treating physician in strict confidence.

10 CHANGES IN CONDUCT OF THE STUDY

10.1 Protocol Amendments

Any change to this Protocol will be documented in a Protocol Amendment, issued by the Sponsor.

Substantial amendments will be submitted for consideration to the approving IECs. An approval is required for a Substantial Amendment, eg, one which could affect the safety of the patients, or which entails a change to the scope/design of the study.

10.2 Premature Termination of Study Sites

The Sponsor reserves the rights to terminate the participation of individual study 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.

11 REPORTING AND PUBLICATION

11.1 Observational Study Report

The data and information collected during this study will be reported in an Observational Study Report prepared by the Sponsor or its designee.

11.2 Confidentiality and Ownership of Study Data

Any confidential information relating to the medicinal product or the study, including any data and results from the study will be the exclusive property of the Sponsor. The treating physician and any other persons involved in the study will protect the confidentiality of this proprietary information belonging to Ferring.

11.3 Publication Policy

At the end of the study, one or more manuscripts for joint publication may be prepared in collaboration between the treating physician(s) offered authorship and Ferring Pharmaceuticals A/S (Ferring) or one of its chosen affiliates. In a multi-site study based on the collaboration of many sites, any publication of results must acknowledge all sites. Results from multi-site studies must be reported in entirety in a responsible and coherent manner, and results from subsets should not be published in advance or without clear reference to the primary entire data. Ferring reserves the right to be last author(s) in all publications related to this study, with a maximum of two employees of Ferring per publication. In the event of any disagreement in the content of any publication, both the treating physician's and Ferring's opinion will be fairly and sufficiently represented in the publication. Any external CRO or laboratory involved in the conduct of this study has no publication rights regarding this study.

If the treating physician wishes to independently publish/present any results from the study, the draft manuscript/presentation must be submitted in writing to Ferring for comment prior to submission. Comments will be given within four weeks from receipt of the draft manuscript. This statement does not give Ferring any editorial rights over the content of a publication, other than to restrict the disclosure of Ferring's intellectual property. If the matter considered for publication is deemed patentable by the Sponsor, scientific publication will not be allowed until after a filed patent application is published. Under such conditions the publication will be modified or delayed at the treating physician's discretion, to allow sufficient time for Ferring to seek patent protection of the invention.

12 ETHICAL AND REGULATORY CONSIDERATION

12.1 Independent Ethics Committee (IEC)

An IEC will review the Protocol and any amendments. The 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 IECs to which the Protocol has been submitted and the name of the committee chairmen will be included in the Observational Study Report.

12.2 Patient Information and Consent

After the treating physician has made the decision to treat the patient with Firmagon or GnRH agonist, the treating physician will obtain a freely given written consent from each patient after an appropriate explanation of the aims and procedures of the study. An English master version of the Patient Information and Informed Consent documents are attached as [Appendix 1]. The study patient must be given ample time to consider participation in the study, before the consent is obtained. The Informed Consent Form must be signed and dated by the patient before he/she is exposed to any study-related procedure, including screening tests for eligibility.

The treating physician will explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify their decision.

The patient will receive a copy of the Patient Information and his signed consent.

Each patient will be informed that representatives from Ferring or regulatory authorities, in accordance with applicable regulatory requirements, may review his source records and data. Data protection will be handled in compliance with national/local regulations.

For patients not qualified to give their legal consent, the written informed consent must be obtained from the legal parent or guardian in accordance with national/local regulations. If such patients can understand the risks and benefits of the study, they should also be informed and provide their written assent.

12.3 Compliance Reference Documents

The Helsinki Declaration, Guidelines for Good Pharmacoepidemiology Practice (GPP; Initially Issued: 1996, Revision 1: August 2004, Revision 2. April 2007), Volume 9A of The Rules Governing Medicinal Products – Guidelines on Pharmacovigilance for Medicinal Product Use (Chapter 7 Company Sponsored Post-Authorisation Studies) and other national laws in the countries where the study takes place shall constitute the main reference guidelines for ethical and regulatory conduct.

13 ARCHIVING

13.1 Site File

The treating physician is responsible for maintaining all the records, which enable the conduct of the study at the site to be fully understood, in compliance with the GPP filing standard. The study documentation including all the relevant correspondence should be kept by the treating physician for at least 5 years after the completion of the Observational Study Report, if no further instructions are given by the Sponsor.

The treating physician 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 e-CRF data for the Sponsor. The treating physician must arrange for the retention of this Patient Identification Log and signed Informed Consent forms for at least 5 years after the completion of the Observational Study Report, if no further instructions are given by the Sponsor.

No study site document may be destroyed without prior written agreement between the treating physician and the Sponsor. Should the treating physician elect to assign the study documents to another party, or move them to another location, the Sponsor must be notified.

13.2 Study Master File

The Sponsor will archive the study master file in accordance with GPP and applicable regulatory requirements.

14 REFERENCES

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15 APPENDICES

[APPENDIX 1] - Patient Information and Informed Consent Documents (English master)

[APPENDIX 2] - Contact Details for SAE Reporting

APPENDIX 1 - PATIENT INFORMATION AND INFORMED CONSENT DOCUMENT TEMPLATE (ENGLISH MASTER)

Informed Consent Documents	[Draft/final] version [no]
[Study Code]	[Date]
[Site no/country]	[No of pages]
[Language]	

A Prospective Observational Safety Study in Patients with Advanced Prostate Cancer Treated with Firmagon® (Degarelix) or a GnRH Agonist

Your physician has decided to treat you with Firmagon or a GnRH agonist for your prostate cancer. These notes will inform you about the study, FE 200486 CS39 which is sponsored by Ferring. If there is anything you do not understand, or if you require further information about any aspect of the study, please do not hesitate to ask the study doctor. Please read these notes carefully before making your decision and keep them safely so you can refer to them during the study.

What is the purpose of this study?

The purpose of this study is to evaluate the long-term safety of Firmagon/GnRH agonist during a 5-year treatment. Firmagon/GnRH agonist is approved for the treatment of patients with advanced prostate cancer. Approximately 1,500 patients will be participating in this study.

Do I have to take part?

Participation in this study is entirely voluntary. It is up to you to decide whether or not to take part. If you decide to take part you will be asked to sign a consent form. However, you are still free to withdraw from the study at any time without giving a reason. A decision not to take part or a withdrawal, will not affect the standard of the care you will receive. If you decide to discontinue, your study doctor will make arrangements for your future care.

What will happen if I decide to take part?

If you decide to take part you will be administered Firmagon/GnRH agonist according to the product labelling. Please refer to the Package Leaflet Information/Patient Counselling Information for additional details about this product. During the course of this study you will have periodic clinical evaluations and blood sampling. These procedures are part of the routine practice in the management and follow-up of patients with prostate cancer.

Will my taking part in the study be kept confidential?

Any information relating to your participation in this study will be treated in the strictest confidence. Representatives of the sponsor may need to look at your medical records to confirm information. Additionally, regulatory authorities and Institutional Review Board / Independent Ethical Committee may need to look at your records to check that the study is being carried out correctly. Your name will not be used outside the hospital and for the purposes of this study you will be identified by the use of a number.

The results of the study will be used for research purposes only. Your personal data may be transferred to data processors located within or outside the European Economic Area / North American Area and may be included in a database or in a publication; however, your identity will remain confidential.

Who can be contacted for further information?

Please contact your study doctor (name and phone number) at any time if you have any questions about the study or if you feel that you are developing a side effect.

Thank you for your interest in this study!

INFORMED CONSENT DOCUMENTS

Signature Page

Screening No:_____ Initials:_____

Country/Language:_____ Centre No:_____

Dr _____ has informed me about the nature and purpose of this study and that the study is sponsored by Ferring Pharmaceuticals A/S.

I am aware of the fact that it is possible for me to withdraw from this study at any point in time without penalty or loss of benefits. Such a decision will not influence my current or future treatment. I am also aware of the fact that the records identifying me will be kept confidential and that my identity will never be disclosed in any publication made as a result of this study.

I agree to allow authorised representatives from Ferring Pharmaceuticals A/S direct access to my original medical records, in order to review and process my data for the purpose of this study and related research. I also consent to authorised representatives from Ferring Pharmaceuticals A/S archiving and transferring my personal data collected during the study to third party data processors. These may be located outside the European Union / North America and accordingly outside the jurisdiction of the EU /North America data privacy legislation. The data collected will only be used for the purpose of this study.

I have read the "Patient Information" [insert version and date of the relevant document] and the "Informed Consent Form" [insert version and date of relevant document], and have been thoroughly informed about the study and I agree to participate in this study.

Patient's Name: _____ _____ _____

Date* Name (print or type) Signature

Impartial Witness

(if applicable): _____ _____ _____

Date* Name (print or type) Signature

*personally dated

The patient will receive a copy of the signed and personally dated Informed Consent Documents (including both the Informed Consent Form and the related Patient Information).

As treating physician, I confirm that the patient was provided with adequate information about the study and that I obtained informed consent from the patient.

Name of treating physician: _____ _____ _____

Date* Name (print or type) Signature

APPENDIX 2 - Contact Details for SAE Reporting

All Serious Adverse Events (SAE) must be reported immediately to:

Global Pharmacovigilance, Ferring Pharmaceuticals A/S

The treating physician will document such events in the best possible details on the SAE Report Form and transmit the form **within 3 calendar days** to the following safety fax number or e-mail address:

Sponsor - Global Pharmacovigilance, Ferring Pharmaceuticals A/S

Contact person	Pharmacovigilance Manager
Address	Global Pharmacovigilance, Att. Safety Mailbox Ferring Pharmaceuticals A/S Kay Fiskers Plads 11 DK-2300 Copenhagen S, Denmark
E-mail	Safety.Mailbox@ferring.com
Fax number	+45 28 17 69 66
Phone number	+45 88 33 88 34