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Statistical Analysis Plan

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
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Date: 08 Aug 2014

STATISTICAL ANALYSIS PLAN

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

(Observational Study)

FE200486 CS39

Medicinal Product: Firmagon® (degarelix powder and solvent for solution for injection)

Indication: Advanced Prostate Cancer

Phase: Observational Study

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Change log

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Role	Name	Position
Author	[redacted]	[redacted], Global Biometrics
Reviewer	[redacted]	[redacted], Consultant (TCS), Global Biometrics
Reviewer	[redacted]	[redacted], Clinical R&D, Urology
Reviewer	[redacted]	[redacted], Global Pharmacovigilance
Reviewer	[redacted]	[redacted] Clinical R&D, Urology
Reviewer	[redacted]	[redacted], Clinical R&D, Urology
Approval	[redacted]	[redacted], Global Biometrics

The document has also been reviewed by [redacted], Clinical R&D, Urology

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1 Introduction

This 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). Prostate cancer 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.

This document describes in details the planned statistical analyses for the FE200486 CS39 study protocol. The original protocol was dated on 25 Nov 2009.

1.1 Definitions of Terms and Abbreviations

1.1.1 Definition of Terms

Terms	Definitions
Enrolled	Patient who has signed informed consent
Month	28 days / 4 weeks
Screened	Patient who enters the screening phase

1.1.2 Abbreviations

Abbreviations	Meaning of abbreviations in document
AE	Adverse Event
AESI	Adverse Event of Special Interest
ADR	Adverse Drug Reaction
ADT	Androgen Deprivation Therapy
ALT	Alanine aminotransferase
CI	Confidence Interval
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
CVD	Cardiovascular Disease
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EoT	End of Trial
GGT	Gamma-glutamyl transferase
GnRH	Gonadotropin-Releasing Hormone
IC	Informed Consent
ITT	Intention-to-treat
KM	Kaplan-Meier
LOCF	Last Observation Carried Forward
mL	Millilitre
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
OC	Observed Case
PCa	Prostate Cancer
PP	Per-Protocol
PSA	Prostate-Specific Antigen
PT	Preferred Term
IRR	Incidence Rate Ratio
SAE	Serious Adverse Event
SD	Standard Deviation
SMQ	Standardised MedDRA Query
SOC	System Organ Class
TE	Treatment Emergent
TEAE	Treatment Emergent Adverse Event
TNM	Tumor, Nodule, and Metastatic
ULN	Upper Level of Normal Range

2 Study Objectives and Endpoints

2.1 Objectives

Primary Objective

The primary objective of this observational study is to describe the risk of the following Adverse Event of Special Interest (AESI) 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 Objectives

The secondary objectives of this Observational study are to:

- Compare the relative risks of the 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

2.2 Endpoints

Safety Endpoints

The following endpoints will be analysed in the study:

1. Rate of 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

3 Study design

This study is a multi-centre, long-term, prospective, observational cohort study to be conducted in 250 countries in Europe. A total of 1500 patients with advanced PCa will be enrolled for participation, including approximately 1000 patients treated with Firmagon and 500 patients treated with a GnRH agonist.

3.1 Schedule of Assessments

Patients will be enrolled after the initial decision (by the investigator) has been made to introduce Firmagon or GnRH agonist as per label indication for prostate cancer. 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.

Since no visits are mandated or prescheduled as part of the study, but collected at visits scheduled as a part of routine care, the changes in hepatic enzymes, fasting serum glucose, testosterone and PSA levels, will be presented by visit intervals as dictated in Section 9.1.1. The reporting date of adverse events will not be changed.

3.2 Study 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 [1]. In an observational study of 73,000 Medicare enrolees with locoregional PCa, Keating et al. [2] 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 [3]. Therefore, the incidence rates in a longer-term observational study are anticipated to be higher. Smith et al [4] 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*	0.98, 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 (with 1000 patients enrolled on Firmagon) is considered sufficient to address the objectives of this Observational study, with reasonable precision.

4 Patient Disposition

All patients screened will be accounted for. All post-treatment allocation discontinuations (withdrawals) will be summarised by duration of study participation and main reason for discontinuation. All major protocol violations and withdrawals from trial will be summarised with frequency and percentage for each category of protocol violation or study discontinuation. The number of patients that were screened, already undergoing treatment when enrolled into the study, completed the trial, withdrew from trial will be summarised. Furthermore, the disposition/attendance of patients by visit-intervals will be provided. The number of patients screened but not allocated to treatment will be presented with the reason(s) for screen failure in a data listing.

In addition, the disposition of patients will be summarised with frequency and percentages after each follow-up visit (3 months interval for first 2 years and 6 months interval remaining 3 years).

Discontinuation rates will be estimated using the Kaplan-Meier (KM) method on time to discontinuation from date of enrolment, and graphically represented in corresponding 1-KM curves, differentiated for reason of discontinuation via cumulative incidence functions. Differences in discontinuation rates will be tested using the Log Rank test (α=0.05, two-sided).

5 Protocol Deviations

Any entered patient meeting one or more of the following criteria will be defined as major protocol violator:

- 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.

These definitions yield at patient level (as opposed to patient and visit level). However, as no analyses are planned for the per-protocol population, there will be no practical implication of these definitions.

6 Analysis Dataset

As the study is non-randomised the intention to treat principle (analyses according to the planned treatment regimen) will not be followed. All analyses will be performed on the actual (received) treatment.

6.1 Safety Analysis Set

The protocol states that “The statistical analyses will be performed on the safety analysis set, which comprises all patients treated with at least one dose of medicinal product.“ Patients who never enter the main treatment period (being dosed and having signed the informed consent (see Section 8) will not be included in the Safety Analysis Set.

7 Study Population

All tabulations and listings will be based on the safety analysis set.

Categorical data will be summarised using numbers and percentages. The percentages are based on the total number of patients with a corresponding assessment relative to the total number of patients in the safety analysis set. Continuous data will be presented using the number of patients (N), mean and standard deviation, median, minimum and maximum. All baseline characteristics will be listed.

In case of study patients enrolled to the Firmagon group are already on the treatment at the time of the baseline visit and baseline data registration, the baseline information will be defined missing as their baseline data may already be affected by the treatment.

Missing values will not be imputed. If the timing of the dose of a concomitant medication cannot be established in relation to the administration of study drug, it will be considered as a treatment emergent concomitant medication (see Section 7.7).

7.1 Demographics

Demographic variables (e.g., age, race and ethnic origin, height, weight and BMI) will be summarised by treatment group.

7.2 Vital Signs at Baseline

Vital signs, as far as collected at baseline, will be summarised by treatment group.

7.3 History and Stage of Prostate Cancer

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

- number of patients diagnosed with PCa
- previous cancer therapies (Radical Prostatectomy, Radiotherapy Neoadjuvant/Adjuvant Hormonal Therapy, and Other)
- ECOG (Eastern Cooperative Oncology Group) performance status, a score in the range of 0 (=fully active) to 4 (=completely disabled)
- Pathological stages of primary tumor (pT) and regional lymph node (pN) (for patients having undergone radical prostatectomy only) (as defined below)
- Gleason score (as defined below)
- stage of prostate cancer (TNM classifications) (as defined below)
- PSA baseline category (as defined below)

The following pathological stages will be recorded and summarized by treatment group:

pT (primary tumor)

- Not done
- Not applicable
- PT2
- PT3MR-
- PT3MR+

pN (regional lymph node)

- Not done
- Not applicable
- PN0
- PN1
- PN2/3

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

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

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

- Localised: T½ & (NX or N0) & M0,
- Locally Advanced: [T¾ & (NX or N0) & M0], or [N1 & M0],
- Metastatic: M1
- Not classifiable: Results from T, N, and M categories that could not be resolved to Localised, Locally Advanced, or Metastatic

The following baseline PSA categories will be used:

- [0-10] ng/mL
-]10-20] ng/mL
-]20-50] ng/mL
-]50-] ng/mL

Dates of diagnosis, and start (and stop) of previous therapies will be presented in patient listings.

7.4 Baseline Risk Factors: Substance Use

The following baseline risk factors for cardiovascular disease and bone fractures / osteoporosis / osteopenia will be summarized (in one table) by treatment group. Frequency of the following activities (amounts will be presented in data listings)

- smoking (categories: Not done / Never / Former / Current)
- alcohol consumption (categories: Not done / Never / Former / Current)
- level of physical activity (categories: Not done / Rare or Never / Monthly / Weekly)

7.5 Dual Energy X-ray Absorptiometry (DEXA) Bone Scan, as Available

Baseline results of bone mass density (BMD) on proximal femur and total lumbar spine, will be summarized by treatment group.

The T-Score compares the bone density to that of young healthy adults in units of standard deviations (SD) [7]. The severity of osteoporosis will be classified based on Table 3. If no T-score is obtained, the severity of osteoporosis is “non-classified”. The number of patients (and percentage) in each category will be tabulated by treatment group.

Table 3: World Health Organization Definitions Based on Bone Density Level [7]

Severity of Osteoporosis	Range in T-Score
Non-Classified	*No T-score present*
Normal	Bone density is within 1 SD (+1 or −1) of the young adult mean.
Low bone mass	Bone density is between 1 and 2.5 SD below the young adult mean (−1 to −2.5 SD).
Osteoporosis	Bone density is 2.5 SD or more below the young adult mean (−2.5 SD or lower).
Severe (established) osteoporosis	Bone density is more than 2.5 SD below the young adult mean, and there have been one or more osteoporotic fractures.

7.6 Medical History

7.6.1 Medical History by MedDRA SMQ Terminology

Medical history recorded at screening visit will be coded using MedDRA and summarised by Primary System Organ Class (SOC) (alphabetically), and Preferred Term (PT) in decreasing order of frequency by treatment.

The following tables will also be presented for the AE in medical history of special interest; i.e. events within the broad scope of the SMQ codes in Appendix 4:

- Medical history of cardiovascular events
- Medical history of diabetes mellitus
- Medical history of fractures
- Medical history of cardiovascular events (explorative analysis)

These tables will be sorted by MedDRA SMQ term (in decreasing frequency of occurrence) and PT (in decreasing frequency of occurrence).

Furthermore, medical history will be presented in patient data listings.

7.6.1.1 Medical History of Events During Pre-consent Period

For the events (defined as in Section 7.6.1) that occur during the pre-consent period, see Section 8, a listing will be prepared with the following contents: subject number; treatment; start date, end date of coded SMQ term; first exposure date; first visit date and date of signed informed consent.

7.6.2 Medical History as Recorded in the eCRF

7.6.2.1 Medical History of Special Interest

Occurrence (yes/no) of medical history of the following risk factors is recorded in the eCRF:

- hyperlipidemia
- hypertension
- diabetes mellitus
- hepatic disorders
- renal disorders
- cardiovascular disease
- osteoporosis

Each category above will be presented by actual number and percentage of total in safety analysis set.

7.6.2.2 Relevant Family History

Occurrence (yes/no) of family history of the following risk factors is recorded in the eCRF:

- prostate cancer

- cardiovascular disease
- diabetes mellitus
- osteoporosis

Each category above will be presented by actual number and percentage of total in safety analysis set.

7.7 Concomitant Medication

Prior and concomitant medication will be summarised by ATC classification 1st level (alphabetically), ATC classification 2nd level (in decreasing order of frequency) and treatment group. These medications will be summarized by treatment for:

1) Prior medication; i.e. medication taken exclusively prior to treatment (i.e. with stop date before date of first drug administration);
2) Concomitant medication, i.e. medication taken during the treatment period (i.e. medication that was not stopped before date of first drug administration and not started after the last drug administration).
3) Post-treatment medications, i.e. medications starting after the treatment period (i.e. with start after the last drug administration).

Furthermore, concomitant medication will be presented in patient data listings.

7.8 Physical Exam

No specific procedures with respect to physical examination are planned as part of the trial. If any physical examination is carried out, and there are any abnormalities at patient level, this data will be listed.

7.9 Explorative Cardiovascular Disease (CVD) Population

The explorative CVD population is defined as those patients with at least one event belonging to the broad scope of any of the following five SMQs: Myocardial infarction; Ischaemic cerebrovascular conditions; Haemorrhagic cerebrovascular conditions; Embolic and thrombotic events, arterial, Other ischaemic heart disease. (Details of SMQ codes are found in Appendix 4.)

One table, presenting the agreement between medical history of cardiovascular disease as reported by the patient (Section 7.6.2.1), and history of cardiovascular disease as identified by the SMQ (Section 7.6.1) will be presented for the overall population.

For the explorative CVD population the following tables will be presented as part of the explorative analysis:

- Demographics as in Section 7.1

- History and Stage of Prostate Cancer, as described in Section 7.3
- Medical History, Section 7.6.

8 Exposure

One of the objectives in the study is to collect AESIs and compare long-term clinical experience with specific important conditions between Firmagon and agonist therapies. The therapy regimens may change, e.g. from continuous treatment to intermittent, at the discretion of the investigator. This section defines exposure periods that are used in order to be able to make unbiased (continuous) treatment comparisons of treatment-emergent adverse events.

8.1 Exposure Periods

In order to limit bias from different treatment effects and overlapping treatment periods on reported adverse events, and to make data comparable to a greater degree, the total exposure period will be partitioned as follows.

At the Baseline Visit patients will be asked if they are on ADT and if so, when it was initiated. The date of Informed Consent is also recorded as part of the eCRF data collection. Start date of *main treatment period* will be considered to be the date at which both the informed consent has been signed, and the first dose has been administered. End date of main treatment period will be recorded as date of loss to follow-up, change in ADT, discontinuation of ADT, or end-of-trial visit, whatever comes first. If treatment continues after end of main treatment period (e.g. due to regimen change), a consecutive treatment period will be considered to be started. Consecutive treatment periods have a similar definition of end-of treatment period as the main treatment period.

In the case that the informed consent was not signed at time of first dosing, a “pre-consent period” is considered. This period ends when the informed consent is signed, at which time the “Main Treatment Period” starts, see Table 4.

Table 4: Exposure periods for a patient dosed prior to signing the informed consent

Event	First Dose of ADT	Signature of IC	Changing treatment regimen
Exposure Period	Pre-consent Period	Main Treatment Period	Post Main Treatment Period

It could also be that the patient signs the informed consent before being dosed. This scenario would lead to the definition of a “Pre-exposure Period”. However, an adverse event occurring before first dose is defined as non-treatment emergent and will not be reported.

Considering AESIs occurring during the "Main Treatment Period" can strengthen the validity of the comparison of the treatment effects on these AEs.

8.2 Extent of Exposure

The extent of exposure (in months of treatment (and in mg)) from start of "Main Treatment Period" to end of last period will be summarised by treatment and presented by descriptive statistics.

Similarly, the extent of exposure (in months of treatment (and in mg)) from start of "Main Treatment Period" to end of "Main Treatment Period" will be summarised by treatment and presented by descriptive statistics. A similar table of the extent of exposure during the "Pre-treatment Period" will be supplied.

Number of subjects in the different periods will be summarized, with percentages relative to the number of subjects in the "Main Treatment Period".

9 Efficacy

The main objectives of this trial are to describe the risk of safety events of special interest. These analysis are described in Section 10. This section describes the analyses of changes in hepatic enzymes, fasting serum glucose, testosterone and PSA levels.

9.1 General considerations

Efficacy parameters will be evaluated for the Safety Analysis Set, see Section 6.1. All statistical tests will be performed using a two-sided test at a 5% significance level.

9.1.1 Visit Window

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 collection windows will be centred on the actual visit dates. The width of the window is +/- 14 days. Should more than one lab data fall into the visit window the following rules will be applied, if possible:

- if a dosing is performed in visit window, the data collected closest in time, prior to the dosing, will be used
- if no dosing is performed in visit window, the median value of the lab data will be used.

9.1.2 Missing Values and Drop-Outs

Data will be presented based on the observed cases. No imputation of missing data (using LOCF or other techniques) is done.

9.1.3 Baseline Data

Baseline data is defined as the non-missing data, closest in time prior to first dose. If no such data is obtained the baseline value will be set to missing.

9.1.4 Change in Fasting Serum Glucose and Serum Hepatic Enzymes from Baseline to Each Visit

Change and percentage change from baseline in glucose and hepatic enzyme levels (alanine aminotransferase, aspartate aminotransferase, bilirubin and alkaline phosphatase) will be summarised by descriptive summary statistics for each treatment arm (median and inter-quartile range) as well as actual values by visit and treatment arm for the analyses set.

9.1.5 Incidence of Glucose Intolerance (Impaired Fasting Glycaemia)

The protocol defines glucose intolerance as a fasting glucose level of 6.1-6.9 mmol/L (110mg/dl-125 mg/dL). (This corresponds to WHO's definition of impaired fasting glycemia [8].) The incidence rate of glucose intolerance will be analysed and presented as described in Section 10.5.1. Adjusting factors will be age, stage of disease and history of diabetes mellitus (as reported by the patient).

9.1.6 Change in PSA from Baseline to Each Visit

Change and percent change of PSA from baseline will be summarised by descriptive summary statistics for each treatment arm (median and inter-quartile range) as well as actual values by visit and treatment arm for the analyses set.

10 Safety

Safety parameters will be evaluated for the Safety Analysis Set, see Section 6.1. The primary endpoints, adverse events of special interest and the primary analyses of these are described in Sections 10.4, and 10.5, respectively.

10.1 General considerations

All statistical tests will be performed using a two-sided test at a 5 % significance level.

AEs will be summarized by treatment group, overall as well as in terms of intensity and relationship to study drug. The handling of missing data will be described for each analysis below.

10.1.1 Table Shell for Adverse Events

To make a balanced comparison with respect to possible differences in drop-out rates, the standard safety table will display the total number (N) of patients exposed, the number of patients reporting an AE, the percentage of patients (%) with an AE, the number of person years, the incidence rate and its 95% CI. The exact uniformly most powerful unbiased test of equal incidence rates will be used to flag significant differences between the two treatment groups.

10.2 Definition of Treatment-Emergent Adverse Events

All adverse events of exposed patients occurring during the “Main Treatment Period” or thereafter (as defined in Section 8) will be considered as treatment-emergent (TE).

Adverse events that occur before first dose (on non-exposed patients) are not defined as treatment emergent and will not be reported.

10.3 Treatment-Emergent Adverse Events

Treatment-emergent adverse events will be classified according to the MedDRA version 15.0 or later. All AEs will be reported.

Adverse events will be classified according to their intensity (using CTCAE v4.02) and relationship to the IMP according to investigator assessment. The number of patients with each AE will be displayed by SOCs (alphabetically) and PT (in decreasing frequency of occurrence).

For patients without an EOT Visit (e.g. due to death), adverse events will be considered treatment emergent if the event occurs within 45 days after the last visit for the patient.

Written narratives will be issued for all serious AEs and AEs leading to withdrawal.

Missing values will be treated as missing, except for causality of AEs to trial drug. If causality is missing, the AE will be regarded as possibly related to trial drug. Related AEs (judged as being reasonably possibly related to trial drug) will be termed ADRs.

10.3.1 Overview of Treatment-Emergent Adverse Events

An AE overview summary table will be prepared for the following categories:

- All AEs
- Deaths
- Serious AEs
- Severe AEs (CTCAE grade 3-5)
- AEs leading to withdrawal

10.3.2 Incidence of Adverse Events

Summary tables of TEAEs by MedDRA SOC (alphabetically) and PT (in decreasing frequency of occurrence) will be prepared for:

- All AEs
- Common AEs (at least 5% of patients)
- AEs by causality
- AEs by intensity
- Serious AEs
- AEs leading to withdrawal
- Non-serious AEs (at least 5% of patients)

Supporting data listings will be provided for:

- All AEs sorted by patient number
- All AEs sorted by MedDRA SOC and PT
- Serious AEs
- AEs leading to death
- AEs leading to withdrawal

10.4 Adverse Events of Special Interest (AESI)

An AESI is a subgroup of general TEAEs and as such are classified and treated as described in Section 10.3.

10.4.1 Definition

The main objective of this observational study is to collect information on AESI. Specifically: cardiovascular events; new onset of diabetes mellitus; progression of osteoporosis or osteopenia; events associated with bone fractures (osteonecrosis); and all-cause mortality. The worsening of glucose intolerance based on lab data has been described in Section 9.1.5. Only events classified as serious will be considered.

Any AESI in the medical history occurring during the "Main Treatment Period" (or thereafter), or any adverse event of special interest in the adverse event report log occurring during the "Pre-consent Period" will be listed, as these possibly should be shifted from medical history to adverse event (or opposite).

In order to limit bias from different treatment effects and overlapping treatment periods and to make data comparable to a greater degree *only* AEs reported during the "Main Treatment Period" are considered (see Section 8.1 for details).

The AEs will be coded using MedDRA lowest level term (LLT). An AE included in any of the following Standardised MedDRA queries (SMQs), at the narrow search scope level, is defined as an event of special interest:

SMQ terms defining a cardiovascular event

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

SMQ term defining new onset diabetes mellitus

- Hyperglycaemia/new onset diabetes mellitus

SMQ term defining worsening of osteoporosis or osteopenia

- Osteoporosis/osteopenia (for incidence of new onset or worsening)

SMQ term for osteonecrosis (bone fracture event)

- Osteonecrosis

Complete lists of SMQ terms and codes are found in Appendix 4.

10.4.2 Incidence of Adverse Events of Special Interest

A summary table will be prepared for the incidence of each AESI. For example, for cardiovascular events, the first AE in the class of the CV SMQs will be accounted for, while the other events will be disregarded. For the incidence rate, it will be the time to this event that is used. Should no event occur, patient is lost to follow-up, or completes the trial (without an event) it is the total observed exposure time that is used, while the patient does not contribute to the derived endpoint count.

10.4.3 Overview of Treatment-Emergent Adverse Events Generating an Event of Special Interest

An overview summary table of TEAEs generating an event of special interest will be prepared for the following categories:

- All AEs
- AEs leading to death
- Serious AEs
- Severe AEs (CTCAE grade 3-5)
- AEs leading to withdrawal

This table will be prepared for each AESI (cardiovascular event, bone fracture, and glucose intolerance).

10.4.4 Incidence of Adverse Events Generating an Event of Special Interest

Summary tables will be prepared for the incidence of the treatment-emergent adverse events generating an event of special interest. The tables will be sorted by

- MedDRA SOC (alphabetically) and PT (in decreasing frequency of occurrence)
- MedDRA SMQ (in decreasing frequency of occurrence) and PT (in decreasing frequency of occurrence).

10.5 Analyses of Adverse Events of Special Interest

10.5.1 Primary Analysis of Adverse Events of Special Interest (AESI)

The mortality rate and respective incidence rates (number of AEs per 100 person years) of each AESI will be estimated using a Poisson regression model. In general, assuming a constant incidence rate of $\lambda_{i,j}$ per unit time for a category *i*, treatment *j* (=0 for GnRH agonist and 1 for Firmagon), the number of events $y_{i,j}$ observed during a time interval of length $t_{i,j}$ (unit 100 years) is distributed as Poisson with mean $\mu_{i,j}=\lambda_{i,j}t_{i,j}$. The mean of a Poisson distributed variable is modelled by

$$log\mu_{i,j} = log\lambda_{i,j} - logt_{i,j} = \alpha + \beta_j + \beta_{i,j}x_{i,j},$$

where $t_{i,j}$ is the number of person years, and *log* $(t_{i,j})$ is modelled as the "offset" with regression coefficient equal to one. Besides the effects of intercept (α) and treatment, modelled by β_j (with GnRH agonist as reference; e.g. β_0=0), the incidence rate (mean) is driven by the adjusting factors for the present category. By this, the adjusted incidence rate ratio (IRR) of an incidence for patients on Firmagon as compared to GnRH agonist is estimated by exp(β_1). For more details, please see page 501 of [5], and page 204 of [6].

Table 5 illustrates data from one treatment arm by each category of adjusting factors (age and stage of disease) used in the model. This example may be extended to include more adjusting factors if required.

Table 5: Data for treatment arm j for Poisson regression

Category	Number of incident events	Patient years (unit 100 years)	Age group	Stage of disease
1	$y_{1,j}$	$t_{1,j}$	<=70	Non-classifiable
2	$y_{2,j}$	$t_{2,j}$	<=70	Localized
3	$y_{3,j}$	$t_{3,j}$	<=70	Locally Advanced
4	$y_{4,j}$	$t_{4,j}$	<=70	Metastatic
5	$y_{5,j}$	$t_{5,j}$	>70	Non-classifiable
6	$y_{6,j}$	$t_{6,j}$	>70	Localized
7	$y_{7,j}$	$t_{7,j}$	>70	Locally Advanced
8	$y_{8,j}$	$t_{8,j}$	>70	Metastatic

The adjusting factors for the four regression models will be

- Age and stage of disease for mortality rates
- Age, stage of disease and cardiovascular history (as reported by the patient) for the incidence of cardiovascular events
- Age, stage of disease and history of diabetes mellitus (as reported by the patient)

for the incidence of events associated with new onset of diabetes mellitus
- Age, stage of disease and history of osteoporosis (as reported by the patient) for the incidence of worsening of osteoporosis or osteopenia
- Age, stage of disease and history of osteoporosis (as reported by the patient) for the incidence of osteonecrosis

Estimated incidence rates for each treatment arm with 95% CI, and IRRs with 95% CI and p-values (based on Wald test) will be provided.

A IRR for treatment with the lower 95% confidence limit >1 may be suggestive of an increased risk of AESI with the use of Firmagon. The IRR with the upper confidence limit <1 may be suggestive of a decreased risk of AESI with the use of Firmagon. If the 95% CI for the IRR includes 1 then the study will be interpreted as failing to establish the difference in risk of AESI between Firmagon and any GNnR agonist treated population.

10.5.2 Time-to-First Event by Kaplan-Meier Methodology

Comparisons between the two treatment arms with respect to time-to death, and time-to first event of special interest, will be based on the log-rank test using the Kaplan-Meier methodology.

Patients who are lost to follow-up before experiencing the adverse event of interest will be censored.

10.5.3 Cox Proportional Hazards Model

Hazard ratios between Firmagon and GnRH agonist (=reference) with respect to death, and (first) event of special interest will be estimated based on the Cox proportional hazard model, adjusted for potential confounding factors as described in Section 10.5.1. Model parameters will be deemed statistically significant assuming a two-sided alpha level of 0.05 based on Wald test for individual parameters.

10.6 Exploratory Cardiovascular Analyses

This section addresses explorative cardiovascular events, defined as Major Adverse Cardiovascular Event (MACE). Analysis will be performed both in the *overall* patient population (Safety Analysis Set), as well as in the *CVD* subgroup, i.e. patients with at least one prior CV event reported in their medical history that was within the *broad* scope search term of any of the five SMQs:

- Myocardial infarction
- Ischaemic cerebrovascular conditions
- Haemorrhagic cerebrovascular conditions
- Embolic and thrombotic events, arterial
- Other ischaemic heart disease

The time to first event for any SAE within the *narrow* scope the five SMQs listed above is defined as the '*time to CV SAE*'. In addition, a combined endpoint defined as *'time to CV SAE* or *death from any cause'* will be analysed. Note that death itself is not an adverse event, but it may be an outcome of an adverse event.

10.6.1 Overview of Treatment-Emergent Adverse Events Classified as a CV SAE

Summary table to be presented as defined in Section 10.4.3. This table will be presented for both overall and subgroup of patients with CVD at baseline.

10.6.2 Overview of Treatment-Emergent Adverse Events Classified as a CV SAE or Adverse Events Leading to Death

Summary table to be presented as defined in Section 10.4.3. This table will be presented for both overall and subgroup of patients with CVD at baseline.

10.6.3 Incidence of Adverse Events Classified as a CV SAE

Summary tables will be prepared for the incidence of the treatment-emergent adverse events classified as a CV SAE. The tables will be sorted by

- MedDRA SOC (alphabetically) and PT (in decreasing frequency of occurrence)
- MedDRA SMQ (in decreasing frequency of occurrence) and PT (in decreasing frequency of occurrence).

Tables will be prepared for both overall and subgroup of patients with CVD at baseline.

10.6.4 Incidence of Adverse Events Estimated with Poisson Regression Model

The primary analysis of Section 10.5.1 will be repeated for the CV SAE. This analysis will be repeated for the CV SAE including death as endpoint, and in the subgroup of patients with prior CVD at baseline. In all, four analyses are planned.

The estimated hazard ratios will (at a minimum) be adjusted for age, stage of prostate cancer and prior CVD (in overall population).

10.6.5 Time-to-First Event by Kaplan-Meier Methodology

Comparisons between the two treatment arms with respect to time-to first event of CV SAE will be based on the log-rank test using the Kaplan-Meier methodology. This analysis will be repeated for the CV SAE including death as endpoint, and in the subgroup of patients with prior CVD at baseline. In all, four analyses are planned.

10.6.6 Cox Proportional Hazards Model

Hazard ratios between Firmagon and GnRH agonist (=reference) with respect to CV SAE will be estimated using the Cox proportional hazard model. Model parameters will be deemed statistically significant assuming a two-sided alpha level of 0.05 based on Wald test for individual parameters.

This analysis will be repeated for the CV SAE including death as endpoint, and in the subgroup of patients with prior CVD at baseline. In all, four analyses are planned.

The estimated hazard ratios will (at a minimum) be adjusted for age, stage of prostate cancer and prior CVD (in overall population) as defined by SMQ terminology.

10.7 Safety Laboratory Variables

There is no planned collection of safety laboratory variables in the study.

10.8 Prostate Cancer Variables

The following variables may be obtained at follow-up visits and will be presented if so.

10.8.1 Change in Prostate Cancer Stage

Change in stage of prostate cancer since last visit is monitored at each follow-up visit, and the outcome is “yes” or “no”. If not performed, “no” change in prostate cancer will be assumed. For each visit, the number of patients with a confirmed change (“yes”) will be tabulated for each treatment arm.

Listings will present the specific change as recorded by the investigator.

10.8.2 Changes in Bone Mass Density

Percentage changes from baseline in bone mass density, if performed, will be tabulated by treatment group and visit.

10.8.3 T-Score

The number of patients (and percentage) in each category accordingly to Table 3 will be tabulated by treatment group and visit.

11 Interim Analyses

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.

12 Deviations from Protocol Analysis

The protocol states that the following endpoints will be analysed:

- Incidence rate of bone fracture, including osteoporotic/fragility fractures
- Incidence rate of new onset or worsening osteoporosis or osteopenia

These endpoints are defined by the following SMQ terms:

SMQ term for osteonecrosis (bone fracture event)

- Osteonecrosis

SMQ term defining worsening of osteoporosis or osteopenia

- Osteoporosis/osteopenia (for incidence of new onset or worsening)

The Statistical Analysis Plan also includes the explorative analyses of cardiovascular adverse events.

13 References

1. [Horner MJ, Ries LAG, Krapcho M, Neyman N, Aminou R, Howlader N, Altekruse SF, Feuer EJ, Huang L, Mariotto A, Miller BA, Lewis DR, Eisner MP, Stinchcomb DG, Edwards BK (eds). *SEER Cancer Statistics Review, 1975-2006*, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2006/, based on November 2008 SEER data submission, posted to the SEER web site, 2009.]
2. [Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol 2006;24:4448-56.]
3. [Shahinian VB, Kuo Y-F, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med 2005;352:154-64.]
4. [Smith MR, Boyce SP, Moyneur E, Duh MS, Raut MK, Brandman J. Risk of clinical fractures after gonadotropin-releasing hormone agonist therapy for prostate cancer. J Urol 2006;175:136-9.]
5. [Armitage, P., Berry, G., Matthews, J.N.S. Statistical Methods in Medical Research, Fourth Edition, Blackwell Science 2002]
6. [McCullagh, P., Nelder, J.A. Generalized Linear Models, Second Edition, Chapman & Hall 1989]
7. [National Institute of Health, Osteoporosis and Related Bone Diseases National Resource Center, Bone Mass Measurement: What the Numbers Mean http://www.niams.nih.gov/Health_Info/Bone/Bone_Health/bone_mass_measure.asp]
8. [World Health Organization, Diabetes Programme, About Diabetes: http://www.who.int/diabetes/action_online/basics/en/index2.html]

14 Table, Listing, and Figures

The tables, figures and listings (TLF) specification document is presented in a separate document.

Appendix 1 Markedly Abnormal Laboratory Safety Values, Vital Signs and ECGs

Table 1: Markedly abnormal Criteria for Laboratory Tests

Variable	Units	Markedly abnormal Criteria	
		Low	**High**
Haematology			
Haemoglobin	g/L	Male: ≤ 115 Female: ≤ 95	Not applicable
Haematocrit	Ratio	Male: ≤ 0.37 Female: ≤ 0.32	≥ 0.56
Total WBC	10^9/L	≤ 2.8	≥ 16.0
Eosinophils	%	Not applicable	≥ 10
Neutrophils	%	≤ 15	≥ 90
Lymphocytes	%	≤ 10	≥ 80
Monocytes	%	Not applicable	≥ 20
Basophils	%	Not applicable	≥ 5
Bands	%	Not applicable	≥ 20
Platelets	10^9/L	≤ 75	≥ 700
Total RBC	10^{12}/L	≤ 3.5	Not applicable
Clinical Chemistry			
AST (SGOT)	IU/L	Not applicable	> 3xUNL
ALT (SGPT)	IU/L	Not applicable	> 3xUNL
Alkaline phosphatase	IU/L	Not applicable	> 3xUNL and 25% increase from baseline
GGT	IU/L	Not applicable	> 3xUNL
LDH	IU/L	Not applicable	> 3xUNL
Total bilirubin	µmol/L	Not applicable	≥ 1.5xUNL
Urea nitrogen	mmol/L	Not applicable	≥ 10.7
Creatinine	µmol/L	Not applicable	≥ 177
Total protein	g/L	≤ 45	≥ 90
Albumin	g/L	≤ 25	≥ 65
Sodium	mmol/L	≤ 130	≥ 155
Potassium	mmol/L	≤ 3.0	≥ 5.8
Chloride	mmol/L	≤ 90	≥ 115
Phosphorus	mmol/L	≤ 0.5	≥ 1.9
Calcium	mmol/L	≤1.8	≥ 3.9
Uric acid	mmol/L	Not applicable	Male: ≥ 0.62

Variable	Units	Markedly abnormal Criteria	
		Low	**High**
			Female: ≥ 0.51
Glucose	mmol/L	≤ 2.8	≥ 10
Total cholesterol	mmol/L	Not applicable	≥ 8.0
Urinalysis: Quantitative			
pH	None	≤ 4	Not applicable
Specific gravity	None	≤ 1.005	Not applicable
Urinalysis: Dipstick Chemistries			
Glucose	0 - 4+	Not applicable	Increase of 2 or more units from baseline
Casts		Not applicable	Increase of 2 or more units from baseline
Protein	0 - 4+	Not applicable	Increase of 2 or more units from baseline
Ketones	0 - 4+	Not applicable	Increase of 2 or more units from baseline
Blood (Hgb)	0 - 4+	Not applicable	Increase of 2 or more units from baseline
Urinalysis: Microscopic Variables			
RBC	no./hpf	Not applicable	≥ 10
WBC	no./hpf	Not applicable	≥ 20
Casts	no./hpf	Not applicable	Neg at baseline to positive on-treatment
Bacteria	no./hpf	Not applicable	Neg at baseline to positive on-treatment
Cells	no./hpf	Not applicable	Neg at baseline to positive on-treatment
Crystals	no./hpf	Not applicable	Neg at baseline to positive on-treatment

Table 2: Markedly abnormal Criteria for Vital Signs*

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

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

Appendix 2 TNM Classification

TNM classification:

Localized:	T 1/2 and (NX or N0) and M0
Locally advanced:	[T 3/4 and (NX or N0) and M0] or [N1 and M0]
Metastatic:	M1

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor.
T1	Clinical inapparent tumor not palpable or visible by imaging.
T1a	Tumor incidental histologic finding in 5% or less of tissue resected.
T1b	Tumor incidental histologic finding in more than 5% of tissue resected.
T1c	Tumor identified by needle biopsy (e.g. because of elevated PSA).
T2	Tumor confined within prostate (tumor found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c).
T2a	Tumor involves one lobe.
T2b	Tumor involves both lobes.
T3	Tumor extends through the prostate capsule.
T3a	Extracapsular extension (unilateral or bilateral).
T3b	Tumor invades seminal vesicle(s).
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles, bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall.

REGIONAL LYMPH NODE (N)

NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Regional lymph node metastasis.

DISTANT METASTASIS (M)

MX	Distant metastasis cannot be assessed.
M0	No distant metastasis.
M1	Distant metastasis.
M1a	Non-regional lymph nodes.
M1b	Bone.
M1c	Other sites.

Appendix 3 ECOG Performance Status

The ECOG performance status will be graded according to the below 5-point scale:

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.

Appendix 4 SMQ codes

The codes followed by an asterix '*' will be used in the tables.

Cardiovascular Events

SMQ Level 1	SMQ Level 2	SMQ code	Considered for Adverse Event of Special Interest	Adverse Event of Special Interest for Explorative Analysis
Cardiac arrhythmias*		20000049	Y	N
Cardiac failure*		20000004	Y	N
Cardiomyopathy*		20000150	Y	N
Central nervous system haemorrhages and cerebrovascular conditions*		20000061	Y	N
Central nervous system haemorrhages and cerebrovascular conditions	Ischaemic cerebrovascular conditions*	20000063	Y	Y
Central nervous system haemorrhages and cerebrovascular conditions	Haemorrhagic cerebrovascular conditions*	20000064	Y	Y
Central nervous system haemorrhages and cerebrovascular conditions	Conditions associated with central nervous system haemorrhages and cerebrovascular accidents*	20000166	Y	N
Embolic and thrombotic events*		20000081	Y	N

SMQ Level 1	SMQ Level 2	SMQ code	Considered for Adverse Event of Special Interest	Adverse Event of Special Interest for Explorative Analysis
Embolic and thrombotic events	Embolic and thrombotic events, arterial *	20000082	Y	Y
Embolic and thrombotic events	Embolic and thrombotic events, venous*	20000084	Y	N
Embolic and thrombotic events	Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous*	20000083	Y	N
Ischaemic heart disease*		20000043	Y	N
Ischaemic heart disease	Myocardial infarction*	20000047	Y	Y
Ischaemic heart disease	Other ischaemic heart disease *	20000168	Y	Y
Torsade de pointes/QT prolongation*		20000001	Y	N

Diabetes Mellitus

SMQ Level 1	SMQ Level 2	SMQ code	Considered for Adverse Event of Special Interest
Hyperglycaemia/new onset diabetes mellitus*		20000041	Y

Osteoporosis or osteopenia

SMQ Level 1	SMQ Level 2	SMQ code	Considered for Adverse Event of Special Interest
Osteoporosis/osteopenia*		20000178	Y

Bone Fractures (Osteonecrosis)

SMQ Level 1	SMQ Level 2	SMQ code	Considered for Adverse Event of Special Interest
Osteonecrosis*		20000180	Y