NON-INTERVENTIONAL PASS PROTOCOL

Title	**Observational prospective study describing the global patient care and follow-up of prostate cancer patients treated with Degarelix** **DUO study (Dialogue in Uro-Oncology)**
Protocol version identifier	000235
Date of last version of protocol	14 February 2017
EU PAS register number	N°18906
Active substance	Degarelix (other hormone antagonists and related agents, ACT code: L02BX02)
Medicinal product	FIRMAGON®
Product reference	Non applicable
Procedure number	Non applicable
Marketing authorisation holder(s)	Ferring SAS
Joint post-authorization safety study (PASS)	Yes MAH contact person: [redacted] Medical Director

Research question and objectives	A consistent increase in risk of Cardiovascular disease for men with prostate cancer (PCa) on GnRH agonists was recently observed during the first 6 months of therapy. This association was particularly strong among men with a history of multiple cardiovascular events, with the most recent event occurring within 1 year before GnRH agonist therapy. The primary objective of the current observational study is to evaluate the prevalence of cardiovascular comorbidities among PCa patients receiving Degarelix before treatment.
Country of study	France
Author	[redacted] E-mail: [redacted]

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	**Ferring SAS** **7, rue Jean-Baptiste Clément** **94250 Gentilly (France)** **Tel:** [redacted]
MAH contact person	[redacted] Medical Director

PROTOCOL SIGNATURE PAGE

Investigator Statement

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects. This study may be terminated by Ferring SAS, with or without cause.

I agree to personally conduct or supervise this investigation and to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments.

I will conduct the study in accordance with Good Pharmacoepidemiology Practices (GPP), the Declaration of Helsinki, and the moral, ethical and scientific principles that justify medical research. The study will be conducted in accordance with all relevant laws and regulations relating to clinical studies and the protection of patients.

I am aware that a copy of the study documents (protocol, patient questionnaire and case report form [CRF] intended for physicians) will be submitted by Ferring SAS to Independent Ethical Committee for information, to the Consultative Committee for the data processing in health research (CCTIRS) for advice and the French Data Protection Agency (CNIL) for approval prior to the study start.

I agree to maintain adequate and accurate records and to make those records available for audit and inspection in accordance with relevant regulatory requirements.

I agree to promptly report to the Sponsor all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without Sponsor approval, except where necessary to ensure the safety of study participants.

Principle Investigator Name:	Pr MONGIAT-ARTUS
Signature:	
Date:	

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2 LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
ADT	Androgen Deprivation Therapy
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical Classification System
BMI	Body Mass Index
CBC	Complete Blood Count
CCAFU	Cancer Committee of the French Urology Association (= *Comité de Cancérologie pour l'Association Française d'Urologie*)
CCTIRS	Consultative Committee for the data processing in health research (= *Comité Consultatif sur le Traitement de l'Information en matière de Recherche)*
CI	Confidence Interval
CNIL	French Data Protection Agency (= *Commission Nationale de l'Informatique et des Libertés*)
CNOM	French National Council of the College of Physicians (= *Conseil National de l'Ordre des Médecins*)
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CVD	Cardiovascular Disease
DCF	Data Clarification Form
DBP	Diastolic Blood Pressure
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMEA	European Medicine Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FPFV	First Patient First Visit
GnRH	Gonadotropin-releasing Hormone
GPP	Guidelines for Good Pharmacoepidemiology Practices

GVP	EMA Guidelines on good pharmacovigilance practices
HAS	French Health Authority (= *Haute Autorité de Santé*)
HDL	High Density Lipoprotein
ICD-10	International Classification of Diseases, Tenth Revision
IEC	Independent Ethics Committee
InVS	French Surveillance Institute (= *Institut de veille sanitaire*)
LDL	Low Density Lipoprotein
LLT	Lowest Level Term
LPLV	Last Patient Last Visit
m	Mean
MedDRA	Medical Dictionary for Regulatory Activities
Mini-GDS	Mini-Geriatric Depression Scale
MRI	Magnetic Resonance Imaging
PCa	Prostate Cancer
PSA	Prostate-Specific Antigen
PT	Preferred Term
QoL	Quality of Life
RCT	Randomized Clinical Trials
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SEC	Self Evident Correction
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
TG	Triglycerides
TNM	Tumor Node Metastasis staging system

3 RESPONSIBLE PARTIES

Ferring SAS is the Sponsor responsible for the overall management of the present study.

The Contract Research Organization (CRO), [redacted] under the supervision of the Ferring SAS, is in charge of the monitoring, data management, biostatistics and protocol writing.

The principal investigator is responsible for ensuring compliance with any study procedures or requirements.

The Scientific Committee shall be the guarantor of the scientific quality of the project and will participate in the early stages of the preparation of the study materials developed to meet its tasks. The Scientific Committee is also charged with maintaining ethical and scientific standards throughout the duration of a research project. It operates in cooperation with the Sponsor, and plays an important role in the protocol review, in providing advice how to conduct the study to ensure that the clinical trial is scientifically sound, and scientific quality of collected data and publication of results is maintained. The Scientific Committee is composed of eight independent persons, highly qualified in the field of uro-oncology.

The Local Safety Officer or Qualified person responsible for pharmacovigilance is responsible for the management of any adverse events reported by the investigators.

The following persons involved in the conduct, analysis or communication of the study are presented in Table 1.

Table 1: Administrative structure of the trial

Function	Name / Location
Scientific Committee Members	[redacted]
Sponsor	FERRING SAS 7, Rue Jean-Baptiste Clément 94250 Gentilly (France) TEL : [redacted]
Medical Director	Dr [redacted] TEL : [redacted] Mail : [redacted]
Head of Scientific and Medical Affairs – Onco-Urology	Dr [redacted] TEL : [redacted] E-mail : [redacted]
Project Leader	[redacted] TEL : [redacted] E-mail [redacted]
Local Safety Officer/ Qualified person responsible for pharmacovigilance	[redacted] TEL : [redacted] E-mail : [redacted]
CRO	[redacted]
Project Manager	[redacted] Phone: [redacted] E-mail : [redacted]
Medical Director	Dr [redacted] E-mail : [redacted]
Medical Director Associate	[redacted] E-mail : [redacted]
Data Management/ Statistical analysis	[redacted] E-mail : [redacted]
Medical writing	[redacted] E-mail : [redacted]

4 ABSTRACT

Title	Observational prospective study describing the global patient care and follow-up of prostate cancer patients treated with Degarelix. DUO study (Dialogue in Uro-Oncology)
Rationale and Background	Eighty percent of all prostate cancers (PCas) are hormone-dependent. Hormone therapy can be envisaged in locally advanced and metastatic cases, working in one of two ways to block testosterone secretion: via either gonadotropin-releasing hormone (GnRH) agonists or GnRH antagonists, such as Degarelix. Following the initiation of hormone therapy, patients often experience "castration syndrome", with effects on cardiovascular, sexual, hematologic, neuropsychological, vasomotor, metabolic and bone functioning (Salomon L, 2013; Rozet F, 2016). Among patients with symptomatic metastatic PCa - considered the primary "target" population for androgenic suppression - associated side effects have generally been considered a secondary concern given the often spectacular benefits of this treatment combined with the typically relatively short treatment duration (with castration resistance tending to occur 18 to 36 months after initiation). Nonetheless, over the last 10 years this balance has shifted dramatically with a significant increase in the number of patients undergoing increasingly long-term androgenic suppression. Collectively, a series of publications by internists, rheumatologists, cardiologists and endocrinologists has drawn treating urologists' attention to the potential side effects of long-term androgen suppression, including osteoporosis (with an increased risk of hip fracture), metabolic syndrome, and development or worsening of diabetes, which lay the groundwork for cardiovascular complications. Consequently, an expert panel of onco-urologists

	(urologists, medical oncologists, radiotherapists) and specialists in the various side effects of androgen suppression (cardiologists, endocrinologists, neuro-gerontologists, psychiatrists, rheumatologists, sexologists) conducted a series of meetings between June 2010 and December 2014 to discuss the effects of long-term androgen suppression. The outcome of these meetings was the publication in 2012 of a series of six articles the French review "Progrès en Urologie" on: - Osteoporotic risk (Cortet B, 2012) - Metabolic impact (Andres E, 2012) - Cardiac risk (Leclercq C, 2012) - Geriatric evaluation (Albrand G, 2012) - Mood and cognitive disorders (Fremont P, 2012) - Sexual disorders (Colson MH, 2012). In addition, a number of the conclusions from these working groups were included in the recommendations published by the Cancer Committee of the French Urology Association (CCAFU) in 2013 and 2016 (Salomon L, 2013. Rozet F, 2016; Cortet B, 2012; Andres E, 2012; Leclercq C, 2012; Albrand G, 2012; Fremont P, 2012; Colson MH, 2012). Furthermore, in conjunction with these reviews, tools for evaluation and follow-up have been made available by Ferring to the French urology community to facilitate the management of potential side effects of androgen suppression. A three-way booklet (for the specialist, treating physician, and patient) was developed by the expert panel to identify at-risk patients on the basis of five areas highlighted by the expert panel: cardiology, metabolism, bones, sexuality, and mood. It was also designed to keep the treating physician up-to-date on appropriate patient follow-up to implement and to offer patient support throughout the treatment duration (patients are given documentation providing information about the treatment, dietary/lifestyle recommendations, and sexual advice). This booklet was made available to the French urology

	community in November 2014. It represents an opportunity to collect epidemiological data on the therapeutic management of side effects of androgen suppression in PCa patients treated with hormone therapy. This is the reason why Ferring decided to implement from his own initiative a study in order to collect these epidemiological data.
Research Question and Objectives:	According to a recent publication (O'Farrell S, 2015), a large observational Swedish study, found a consistent increase in risk of cardiovascular disease for men with PCa on GnRH agonists. This increase was observed during the first 6 months of therapy. This association was particularly strong among men with a history of multiple cardiovascular events, with the most recent event occurring within 1 year before GnRH agonist therapy. The primary objective of the current observational study is to evaluate the prevalence of cardiovascular comorbidities among PCa patients receiving Degarelix before treatment. The secondary objective is to evaluate the prevalence of osteoporotic and metabolic comorbidities, of mood and sexual disorders, as well as the geriatric comorbidities in elderly patients, among PCa patients receiving Degarelix. The third objective is to evaluate compliance with recommendations made by the expert group and the CCAFU through the use of practical tools made available to the patient and his treating physician. This study also aims to describe patient characteristics at the Degarelix therapy is initiated, and the care and quality of life (QoL) of PCa patients receiving Degarelix, in order to provide real-life data of the impact of Degarelix treatment after 6 months.
Study Design:	Referring to Appendix 1 of the EMA GVP on Post-authorisation studies (Module VIII) and to Guidance in the ENCePP Guide for Methodological Standards for further details on PASS study design, this study is an observational, longitudinal, pharmaco-epidemiological, multicenter, prospective cohort study.

	Physician selection will be performed according to the following successive steps: A letter requesting participation along with a response slip will be sent to all urologists (French medical urologists practicing in a hospital setting (approximately 1,200), either in a private clinic or with a dual activity principally hospital-based, treating PCa patients who are eligible for hormone therapy) and all physicians of the DUO Expert Panel. - Physicians return the response slip to the study contract research organization (CRO). - Non-responding physicians will be called by the study CRO. - All interested physicians will be sent a Participation Agreement Form, along with their chosen financial agreement, with a personalized contract. - Physicians will return their signed financial agreement. - Initiation visit by phone with the site after the kits have been sent. We estimate that approximately: - 120 (~10%) eligible physicians will be interested in participating in the study on the basis of the initial information letter received by mail and the follow-up phone call. - 60 (~50% of eligible physicians) physicians will provide written confirmation of their participation in the study. - 50 physicians will participate actively in the study. <u>Modalities of patient recruitment</u>: It is anticipated that 170 patients fulfilling the inclusion criteria will be consecutively included by participating physicians over 12-month inclusion period. Recruited patients will be followed up for 6 months (±1 month) after treatment initiation. Patients withdrawing from the study before study end, lost to follow-up, who move, change medical teams, or die will

	be documented as having early study withdrawal in the electronic Case Report Form (eCRF). As a non-interventional study, all data will be collected during routine follow-up visits scheduled by physicians. Only data available in patients' medical files and other items that are evaluated as part of routine disease management will be collected. All medications will be prescribed at the participating physicians' discretion and will not be influenced by the study procedures. The adverse event (AE) will be collected as a PASS study (see primary and secondary objectives). The medical prescription will be left solely to the initiative of the participating centres, and only patients for whom the physician himself has decided to prescribe Degarelix will be enrolled in the study. The reporting of AEs is thus subject to the terms of Good Pharmacoepidemiology Practices, updated on June, 2015, which includes an obligation of reporting by any physician who suspects a serious or unexpected adverse drug reaction whether or not he has prescribed the medication. The study will be implemented for the 60 eligible specialists. Prior to including a patient, the physician will explain the objectives of the study and inform the patient of his rights both orally and in writing using a specific Patient Information Sheet. Before inclusion, patients should sign the Consent Form.
Population:	The study will be conducted by French Urologists from Q4 2016 (site selection) to Q3 2018 (last patient last visit); 50 active sites located in France will be planned to include 170 eligible patients. **Main criteria for inclusion/exclusion :** <u>Inclusion Criteria</u> : - Male aged 18 years or older - Diagnosed with hormone dependant advanced prostate cancer PCa - Patient having received an antagonist of GnRH Degarelix prescription

	- Agreeing to and capable of completing in French during the visits all questionnaires on the impact of their illness and treatment - Patients having received oral and written study information, agreeing to the use of his anonymized data, and having signed a written Informed Consent Form Exclusion Criteria : - Patient included in an interventional study assessing treatment for PCa - Patient presenting hypersensitivity to Degarelix or one of its excipients - Patient treated by other hormonotherapy **NB:** ***it is important that patients are naive of hormone therapy to have objective epidemiological data of different comorbidities, including cardiovascular comorbidities.*** **Withdrawal Criteria:** Patients may withdraw consent at any time. If a patient is withdrawn prior completion of the study or follow- up period, any reason for withdrawal will be documented in the database, when 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 or guardian and no additional information will be entered in the study database.
Variables:	**OBJECTIVES :** The objectives will be evaluated using data entered in the eCRF and collected from the eCRF provided to physicians (for clinical data) and patients questionnaire (for quality of life data), when available, given the non-interventional nature of the study. **Primary objective :** To describe the prevalence of the cardiovascular comorbidities, at the initiation of Degarelix, in PCa patients. **Secondary objectives:**

	1- To describe, at the initiation of Degarelix, the real-life prevalence of metabolic comorbidities, osteoporotic comorbidities, mood and sexual disorders as well as the geriatric comorbidities in elderly patients (geriatric oncology) in PCa patients. 2- To describe patient characteristics at the time Degarelix is initiated. 3- To evaluate real-life prevalence of the comorbidities after 6 months of follow-up. 4- To describe the therapeutic management of PCa patients receiving Degarelix, in order to provide real-life data of the impact of hormone treatment after 6 months. 5- To evaluate compliance with recommendations made by the CCAFU through the use of practical tools made available to the patient and his treating physician. 6- To describe the QoL of PCa patients receiving androgenic suppression hormone therapy, at inclusion and after 6 months of follow-up, and to compare QoL in terms of the presence or not of comorbidities. 7- To evaluate tolerance in PCa patients receiving Degarelix hormone therapy using real-life data from all AE over the 6-month period (data collection for comorbidities). **ENDPOINTS :** **Primary endpoint :** A patient will be considered to have cardiovascular comorbidities if he has a history of at least one cardiovascular illness and/or at least three cardiovascular risk factors. *The following data will be collected :* - *Clinical examination : weight, height, BMI, waist circumference,* - *History of cardio-neuro-vascular disease according to International Classification of Diseases, Tenth Revision [ICD-10]: number of cardiovascular disease among cerebrovascular accident or stroke [neurologist-*

	certified], myocardial ischemia or infarction, coronary artery disease [cardiologist-certified], angina pectoris, heart failure [cardiologist-certified], peripheral artery disease, arrhythmia, etc., - *Number of cardiovascular risk factors (recommendations published by the Cancer Committee of the French Urology Association (CCAFU) in 2013 and 2016,* - *Current medications (cardiac [angina, heart failure, etc.]),* - *Clinical examination (systolic/diastolic blood pressure),* - *Implementation of a cardiologist assessment.* **<u>Secondary endpoints :</u>** The endpoints for each secondary objectives are : 1- To describe the real life prevalence of comorbidities : **<u>For metabolic comorbidities:</u>** A patient will be considered to have metabolic comorbidities if he has a history of at least one metabolic disease. *The following data will be collected : lipid disorders, and/or diabetic, lipid profile (total cholesterol, triglycerides [TG], High Density Lipoprotein [HDL] - Low Density Lipoprotein [LDL]) and glycemic blood tests, clinical examination (weight, height, BMI, waist circumference), metabolic syndrome, dietary/lifestyle measures (in place or to be implemented), and implementation of an endocrinologist assessment.* **<u>For osteoporotic comorbidities</u>**: A patient will be considered to be with osteoporotic comorbidities if he presents a more than 20% risk of major fracture at 10 years, and/or a more than 3% risk of hip fracture at 10 years and/or a T-score < -2. *The following data will be collected :* *Number of osteoporosis risk factors, history of falls, blood tests (creatinine, vitamin D) within normal ranges, full calcium/phosphorus blood tests (yes/no), evaluation of the risk of fracture with the FRAX score, osteodensitometry*

	(bone mineral density), and evaluation of T-scores, prescription of daily vitamin D, and implementation of a rheumatologist assessment. **<u>For elderly patients</u>:** A patient will be considered to be with geriatric comorbidities if he is more than 70 years old and has a G8 score ≤ 14. *The following data will be collected :* *Onco G8 questionnaire (score) and implementation of a geriatric and/or onco-geriatric specialist assessment.* **<u>For mood disorders</u>:** Patient will be considered to be with depression risk comorbidities if his mini-GDS score is ≥ 1. *The following data will be collected :* *Mini-Geriatric Depression Scale (mini-GDS) (score), patient concerns, and implementation of a psychiatrist or general physician assessment.* **<u>For sexual disorders</u>:** Patient will be considered to be with sexual disorder comorbidities if he has erectile dysfunction, and/or ejaculation dysfunction, and/or pain or discomfort, and/or concerns over his desire or sex life. *The following data will be collected :* *Erection or ejaculation dysfunction, pain or discomfort, concerns over desire or sex life, satisfaction with sex life (yes/no), sexual activity, Tessler, DAN-PSS, UROLIFE questionnaires, and implementation of a sexologist assessment.* 2- To describe patient characteristics : - Patient demographic data - Family history - Blood tests - Cancer diagnosis - Tumour stage - PSA levels

	- Testosterone levels - Concomitant medications *The following data will be collected :* - *Patient initials - Date of inclusion visit* - *Verification of provision of Patient Information Sheet/Informed consent* - *Patient demographic data: date of birth, professional status, marital status* - *Cigarette and alcohol consumption* - *Medical history and Family history of cancer* - *Hemoglobunemia* - *Date of cancer diagnosis (biopsy)* - *Biopsy: sites, number of samples* - *Tumour stage at diagnosis (Tumor Node Metastasis staging system [TNM] classification) and prognostic factors (Gleason score)* - *Prostate-specific Antigen (PSA) (ng/mL) and testosterone (ng/mL) levels* - *Dose and duration of prior and ongoing treatments for PCa* - *Drug class and duration of concomitant medications excluding PCa treatments (indication)* - *Digital rectal examination (Yes/No)* - *CT scan (Yes/No and reason)* - *Magnetic resonance imaging (MRI): (Yes/No and reason); extraprostatic spread (Yes/No)* - *C-choline PET/CT scan (Yes/No)* 3- To evaluate real-life prevalence of the comorbidities after 6 months of follow-up : Modification of the comorbidities after 6 months (cardiac, metabolic, osteoporotic, geriatric, mood and sexual disorders). *The following data will be collected :* - *For cardiac comorbidities: changes in cardiovascular risk factors or cardiac concomitant medications, major cardiovascular events, changes in clinical examinations*

	(systolic/diastolic blood pressure), follow-up by a cardiologist. - *For metabolic comorbidities: new lipid or glycemic abnormalities, changes concomitant medications, changes in clinical examinations (body mass index [BMI], waist circumference), occurrence of metabolic syndrome, occurrence or continuation of poor dietary/lifestyle measures, follow-up by an endocrinologist.* - *For osteoporotic comorbidities: change in the number of osteoporosis risk factors, falls events, osteoporotic events, blood tests (creatinine, vitamin D) within normal ranges, change in the risk of fracture with the FRAX® score, change in the prescription of daily vitamin D intake and/or supplementation, follow-up by a rheumatologist.* - *For elderly patients (≥ 70 years): falls and lost autonomy assessment, follow-up by a geriatric and/or an onco-geriatric specialist.* - *For mood disorders: mini-GDS (score), patient concerns, follow-up by a psychiatrist or a general physician.* - *For sexual disorders: changes in erection or ejaculation dysfunction or in pain or discomfort, concerns over desire or sex life, change in Tessler, DAN-PSS, UROLIFE scores, follow-up by a sexologist.* 4- To describe the therapeutic management : - Tumor evaluation (TNM), examinations and Biological modification - All treatments for PCa over the 6-months period *The following data will be collected :* - *Visit date* - *Cigarette and alcohol consumption* - *PSA (ng/mL) and testosterone (ng/mL) data after 3 and 6 months* - *TNM* - *Extraprostatic spread (Yes/No)*

	- *All treatments for PCa over the 6-months period (modifications to ongoing treatments, dose, treatment duration)* 5- To evaluate compliance with recommendations : Percentage of patients whom benefits of the practice tools. 6- To describe the QoL of PCa patients : QoL evolution during 6 months treatment. *The following data will be collected :* *EQ5D at inclusion and after 6 months treatment.* 7- To evaluate tolerance : Percentage of patients with at least one adverse event and adverse events description. *The following data will be collected :* *All AE collected during the study period.*
Data Sources:	All data will be collected during routine follow-up visits scheduled by physicians in clinical practice. Only data available in patients' medical files and other items that are evaluated as part of routine disease management will be collected. The physician will complete a register for all consecutively patients initiating Degarelix treatment who meet the inclusion criteria. For patients not included, the reason of non-inclusion will be collected in the register.
Study Size:	It is planned that 170 patients fulfilling the inclusion criteria will be consecutively included by participating physicians over a 12-month period. <u>Sample size determination</u>: The primary objective of the study is to estimate the prevalence of cardiovascular comorbidities. The 95% confidence interval (95% CI) was used to justify the number of required patients. According to the literature

	(Leclercq C, 2012; Albrand G, 2012; Fremont P, 2012; Colson MH, 2012; O'Farrell S, 2015), the prevalence of cardiovascular comorbidities (at least one prior event) is estimated from 15% to 25%. According to these hypotheses, 170 PCa patients eligible to receive androgenic suppression hormone therapy are required for a true prevalence of 20% and a Standard Error of the prevalence estimate of 3%.With 170 patients, width of the corresponding 95% Confidence Interval is then approximately 12% which is deemed sufficient for the trials purpose. The 95% two-sided CI is expected to be [8%; 32%].
Data Analysis:	The prevalence of cardiovascular comorbidities will be described along with the 95% CI. Note: The method of physician selection will not ensure sample representativeness, and furthermore physicians can refuse to participate in the study. Sample representativeness will thus be determined by comparing the initial sample of the Sponsor's national database of sites with the sample of active sites. All results should be interpreted cautiously. In addition, as part of an observational study with prospective cohort study evaluated over a 6-months period, it is important to take into account the handling of missing data for the primary endpoint when considering the accuracy of estimation and relevance of the study results. Nonetheless, because the primary objective is evaluated at baseline, this bias should be reduced.
Milestones:	- Regulatory submission: Q3 2016 - Site selection: Q4 2016 - Q1 2017 - Inclusion period: Q2 2017 – Q2 2018 - Last patient last visit: Q4 2018 - Database lock: Q1 2019 - Statistical analyses: Q2 2019 - Final report: Q3 2019

5 AMENDMENTS AND UPDATES

None.

6 MILESTONES

Planned dates for study milestones are indicated in the Table *2* below.

Table 2: Summary of Study Milestones

Milestone	**Planned date**
Regulatory submission	September 2016 – February 2017
Site selection	November 2016 - March 2017
Inclusion period	May 2017 - April 2018
Start of data collection	May 2017
End of data collection (Last patient last visit)	November 2018
Database lock	January 2019
Statistical analyses	April 2019
Final report of study results	September 2019

7 RATIONALE AND BACKGROUND

In France, prostate cancer (PCa) is the most commonly reported cancer in men (56,800 new cases per year in 2012) followed by the lung and colo-rectal cancers (Institut National de veille sanitaire (INVS), 2013 juil 11), and represents the fourth cause of death by cancer with 8,876 deaths per year in 2012 (INCa, 2016). Since 2005, incidence of PCa decreased, and the trends are encouraging with improvement in survival at 5 years: 94% between 2005 and 2010 with an increase of +22 points from 1989 to 1993 (72%) (Institut National de veille sanitaire (INVS), 2013 juil 11).

PCa is most frequently diagnosed by a rise of the total serum Prostate-specific Antigen (PSA) value, abnormality in prostate consistency detected by rectal examination or more rarely after pathological examination of the tissue removed during the management of a benign prostatic hyperplasia. The diagnosis is confirmed by histological examination of transrectal biopsy samples guided by transrectal ultrasound (Haute Autorité de Santé (HAS), 2015).

Eighty percent of all PCas are hormone-dependent. Hormone therapy can be envisaged in locally advanced and metastatic cases, working in one of two ways to block testosterone secretion: via either gonadotropin-releasing hormone (GnRH) agonists or GnRH antagonists, such as Degarelix. The major advantage of the GnRH antagonists by blocking the LHRH receptors is the absence of biochemical flare, a transient increase in testosterone associated with the initiation of androgen deprivation therapy (ADT) (Uhlman MA, 2009; Klotz L, 2008).

Following the initiation of hormone therapy, patients often experience “castration syndrome”, with effects on cardiovascular, sexual, hematologic, neuropsychological, vasomotor, metabolic and bone functioning (Salomon L, 2013; Rozet F, 2016).

Among patients with symptomatic metastatic PCa - considered the primary “target” population for androgenic suppression - associated side effects have generally been considered a secondary concern given the often spectacular benefits of this treatment combined with the typically relatively short treatment duration (with castration resistance tending to occur 18 to 36 months after initiation). Nonetheless, over the last 10 years this balance has shifted dramatically with a significant increase in the number of patients undergoing increasingly long-term androgenic suppression.

Collectively, a series of publications by internists, rheumatologists, cardiologists and endocrinologists has drawn treating urologists’ attention to the potential side effects of long-term androgen suppression, including osteoporosis (with an increased risk of hip fracture) (Morote J, 2007), metabolic syndrome, and development or worsening of diabetes, all of which lay the groundwork for cardiovascular complications (Saylor PJ, 2009).

Consequently, an expert panel of onco-urologists (urologists, medical oncologists, radiotherapists) and specialists in the various side effects of androgen suppression (cardiologists, endocrinologists, neuro-gerontologists, psychiatrists, rheumatologists, sexologists) conducted a series of meetings between June 2010 and December 2014 to discuss the effects of long-term androgen suppression.

The outcome of these meetings was the publication in 2012 of a series of six articles in the French review “Progrès en Urologie” on:

- Osteoporotic risk (Cortet B, 2012)
- Metabolic impact (Andres E, 2012)
- Cardiac risk (Leclercq C, 2012)
- Geriatric evaluation (Albrand G, 2012)
- Mood and cognitive disorders (Fremont P, 2012)
- Sexual disorders (Colson MH, 2012).

In addition, a number of the conclusions from these working groups were included in the recommendations published by the Cancer Committee of the French Urology Association (CCAFU) in 2013 and 2016 (Salomon L, 2013; Rozet F, 2016; Cortet B, 2012; Andres E, 2012; Leclercq C, 2012; Albrand G, 2012; Fremont P, 2012; Colson MH, 2012).

Furthermore, in conjunction with these reviews, tools for evaluation and follow-up have been made available by Ferring to the French urology community to facilitate the management of potential side effects of androgen suppression. A three-way booklet (for the specialist, treating physician, and patient) was developed by the expert panel to identify at-risk patients on the basis of five areas highlighted by the expert panel: cardiology, metabolism, bones, sexuality, and mood. It was also designed to keep the treating physician up-to-date on appropriate patient follow-up to implement and to offer patient support throughout the treatment duration (patients are given documentation providing information about the treatment, dietary/lifestyle recommendations, and sexual advice).

This booklet was made available to the French urology community in November 2014. It represents an opportunity to collect epidemiological data on the therapeutic management of side effects of androgen suppression in PCa patients treated with hormone therapy. This is the reason why Ferring decided to implement from his own initiative a study in order to collect these epidemiological data.

8 RESEARCH QUESTION AND OBJECTIVES

According to a recent publication (O'Farrell S, 2015), a large observational Swedish study, found a consistent increase in risk of cardiovascular disease for men with PCa on GnRH agonists. This increase was observed during the first 6 months of therapy. This association was particularly strong among men with a history of multiple cardiovascular events, with the most recent event occurring within 1 year before GnRH agonist therapy.

Among therapies, Degarelix is a GnRH receptor blocker (antagonist) which has been developed for patients with PCa who need ADT. It has been shown in a comparative, randomized, open-label, parallel group that Degarelix was not inferior to leuprolide at maintaining low testosterone levels over a 1-year treatment period in patients with PCa (Klotz L, 2008). Associations of baseline cardiovascular disease risk profile, dosing regimen and treatment duration with incident cardiovascular disease events during ADT with Degarelix (20 to 480 mg for an average of 22 months) were previously investigated in 1,704 men with PCa after having pooled data from 9 clinical trials. This study suggested that

observed rates of cardiovascular disease events were similar before and after Degarelix treatment in the total population (5.5 vs 6.1/100 person-years, p=0.45) and in men without cardiovascular disease (5.6 vs 4.3/100 person-years, p=0.11) (Smith MR, 2011; Haute Autorité de Santé (HAS), 2015). In addition, Albertsen et al. concluded that GnRH antagonists appeared to halve the number of cardiac events experienced by men with preexisting cardiovascular disease during the first year of ADT when compared to GnRH agonists (HR=0.44; IC95% of [0.26; 0.74]; p=0.002) (Albertsen PC, 2014; Haute Autorité de Santé (HAS), 2015). As off-label regimens of Degarelix were used in these both studies, further investigations are necessary to assess whether prevalence of cardiovascular morbidity differs following initiation of gonadotropin-releasing hormone (GnRH) antagonists. Moreover, data regarding cardiovascular, osteoporotic, metabolic, geriatric, mood and cognitive, sexual comorbidities of patients before treatment for advanced PCa are limited in the literature.

Thus, the main and secondary objectives of this study are as follows:

Primary Objective :

The primary objective of the current observational study is to evaluate the prevalence of cardiovascular comorbidities among PCa patients receiving Degarelix before treatment.

Secondary Objectives :

- To describe, at the initiation of Degarelix, the real-life prevalence of metabolic comorbidities, osteoporotic comorbidities, mood and sexual disorders as well as the geriatric comorbidities in elderly patients (geriatric oncology) in PCa patients,
- To describe patient characteristics at the time Degarelix is initiated,
- To evaluate real-life prevalence of the comorbidities after 6 months of follow-up,
- To evaluate compliance with recommendations made by the expert group and the CCAFU through the use of practical tools made available to the patient and his treating physician,
- To describe the therapeutic management of PCa patients receiving Degarelix, in order to provide real-life data of the impact of hormone treatment after 6 months,
- To describe the QoL of PCa patients receiving androgenic suppression hormone therapy, at inclusion and after 6 months of follow-up, and to compare QoL in terms of the presence or not of comorbidities described in the primary and secondary objectives,
- To evaluate tolerance in PCa patients receiving Degarelix hormone therapy using real-life data from all AE will be collected over the 6-month period (data collection for comorbidities).

9 RESEARCH METHODS

9.1 Study Design

The study will be an observational, longitudinal, multicenter, prospective cohort, post-authorization safety study (PASS).

This will be a non-interventional study conducted in advanced PCa adult patients for whom the investigator will decide to prescribe a treatment with Degarelix. All data will be collected during routine follow-up visits scheduled by physicians. Only data available in patients' medical files and other items that are evaluated as part of routine disease management will be collected. All medications will be prescribed at the participating physicians' discretion and will not be influenced by the study procedures.

The study will be planned to be implemented by 60 eligible specialists (50 active physicians) among a sample of French urologists supporting PCa patients eligible for hormone therapy and all physicians of the DUO Expert Panel.

Physicians' selection

Physicians' selection will be performed according to the following successive steps:

An information letter requesting participation along with a response slip will be sent to all French medical urologists estimated at 1,200 practicing in a hospital setting, either in a private clinic or with a dual activity principally hospital-based, treating PCa patients who are eligible for hormone therapy and all physicians of the DUO Expert Panel.

If interested in participating to the study, physicians will be asked to complete the response slip and to return it to the study contract research organization (CRO) in charge of the conduct of the study. Regarding the non-responding physicians, they will be contacted by phone by the CRO for recruitment, and to report the possible reasons in case of refusal. Considering that the usual acceptance rate of eligible physicians on the basis of the initial information letter received by mail and the follow-up phone call is about 10%, the number of physicians interested in participating in the study is estimated at 120.

All interested physicians will receive a Participation Agreement Form, along with their chosen financial agreement, with a personalized contract, and will validate their participation by signing and returning their signed financial agreement to the CRO. It will be estimated that approximately 60 (~50% of eligible physicians) physicians will provide written confirmation of their participation in the study.

After the receipt of the Participation Agreement Form, the study kits will be sent to the physician, and an initiation visit was performed by phone with the site. A total of 60 physicians will be expected in the study.

Active physicians will be asked to complete a "physician's Questionnaire" including the following data:

- Age, gender
- Length of practice
- Type of practice
- Location of practice (department and size of the town of practice).

Modalities of patient recruitment:

It is anticipated that 170 patients fulfilling the inclusion criteria will be consecutively included by participating physicians over an inclusion period of 12 months.

The recruitment will be competitive in order to avoid potential bias of selection.

Recruited patients will be followed up for 6 months (± 1 month) after treatment initiation.

The medical prescription will be left solely to the initiative of the participating centres, and only adult patients with advanced PCa meeting the inclusion/exclusion criteria for whom the physician himself has decided to prescribe Degarelix will be enrolled in the study.

Prior to including a patient, the physician will explain the objectives of the study and inform the patient of his rights both orally and in writing using a specific Patient Information Sheet. Before inclusion, patients should sign the Consent Form.

The physician will complete a register (Annex 7) for all consecutively patients initiating Degarelix treatment who meet the inclusion criteria. For patients not included, the reason of non-inclusion will be collected in the register.

Rationale of the study design

The descriptive and non-interventional study design was chosen to provide real-life data of the impact of Degarelix treatment during a 6-month initiation period in patients suffering from PCa at an advanced stage. The strength of the study design to answer the research question may be related to the design of the study. This non-interventional design seemed the most appropriate to evaluate the prevalence of safety concerns (cardiovascular, osteoporotic, geriatric and metabolic comorbidities, mood and sexual disorders) after its marketing authorization and usual measures taken reflecting current medical practice in terms of treatment monitoring and care of advanced PCa. Indeed, patients at high risk of adverse effects, medically fragile or with multiple comorbidity are often excluded from randomized clinical trials (RCTs). Therefore, identification of rare adverse events (AEs) is difficult as RCTs often do not use big enough population sample or do not have adequate follow-up. In order to overcome these limitations, a big amount of data from observational studies is often taken in consideration for the safety-profile evaluation of a particular intervention. In this study, the AE will be collected as a PASS study (see primary and secondary objectives). The reporting of AEs is thus subject to the terms of Good Pharmacoepidemiology Practices, updated on June 2015, which includes an obligation of reporting by any physician who suspects a serious or unexpected adverse drug reaction whether or not he has prescribed the medication.

9.1.1 Schedule of Assessments

According to the routine practice, the study assessments are provided in Table 3.

Table 3: Study Flowchart

Visits ▶ Data collected ▼	Inclusion/ Prescription	Data collected 6 months post-prescription*
Verification of inclusion/exclusion criteria	X	
Study information and patient informed consent [(a)]	X	
Demographics [(b)] and clinical examination (SBP, DBP)	X	X
Medical history and family history of cancer	X	
Information on PCa [(c)]	X	X
Comorbidities (evaluation of each risk factor)[(d)]	X	
Smoking and alcohol consumption	X	X
Blood tests [(e)]	X	X
Prescription of hormonotherapy	X	
Previous and concomitant treatments	X	X
Follow-up data for each risk factor		X
Patient QoL (EQ5D) questionnaire	X	X
Adverse events (AEs)		X
Reason for study withdrawal [(f)]		X

Systolic blood pressure (SBP), Diastolic blood pressure (DBP)
* 6 months: As a non-interventional study, all data will be collected during the visit scheduled by physician around month 6.
(a) Written informed consent must be obtained prior to any study related data collection.
(b) Date of birth, professional status, and marital status.
(c) Date of PCa diagnosis, biopsy, Gleason score, and digital rectal examination at inclusion, and Tumor Node Metastasis staging system (TNM) classification, PSA and testosterone, CT scan, magnetic resonance imaging (MRI), extra-prostatic spread, and C-Choline PET/CT scan at both baseline and over the 6-month follow-up period.
(d) Cardiovascular, metabolic, osteoporotic, geriatric comorbidities and mood and sexual disorders.
(e) Hemoglobinemia, total cholesterol, triglycerides (TG), High density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol, glycemic blood tests, creatinine, vitamin D, full calcium/phosphorus blood tests.
(f) Patient wishing to withdraw from the study, patient lost to follow-up (date of last contact), patient moved or changed of medical team, or withdrawal due to another reason should be specified.

Data will be collected by the physician during up to two visits:

- V1: Inclusion
- V2: Follow-up (up to 6 months post-enrolment)

9.1.2 V1: Baseline – Inclusion

A treatment with Degarelix will be prescribed by the Investigator for initiation. The medical prescription will be left solely to the initiative of the participating centres, and only patients for whom the physician himself has decided to prescribe Degarelix will be enrolled in the study.

Following evaluation and checks of inclusion/exclusion criteria by the investigator, patients presenting with advanced PCa who meet the inclusion and exclusion criteria will be eligible for

inclusion in the study. Prior to the inclusion of a patient, the physician will explain the objectives of the study and inform the patient of his rights both orally and in writing using a specific Patient Information Sheet. Before inclusion, patients should sign the Consent Form if he agrees to participate to the study.

The physician will complete a register (Annex 7) for all consecutively patients initiating Degarelix treatment who meet the inclusion criteria. For patients not included, the reason of non-inclusion will be collected in the register.

During this baseline visit, the following data, as recommended by current treatment guidelines, will be collected from the investigator/medical record such as: demographics, clinical data, medical history and family history of PCa and breast cancer, information on PCa (date of diagnosis, biopsy, TNM classification, Gleason score, PSA and testosterone, digital rectal examination, radiologic examinations), smoking habits and alcohol consumption, comorbidities including all data for each risk factor information towards with cardiovascular, metabolic, osteoporotic, geriatric comorbidities and mood and sexual disorders, dose and duration of previous and concomitant treatments. The patient underwent blood tests. All results from these laboratory tests will be collected by the Investigator in the eCRF.

At the time of inclusion, one standardized and validated health questionnaires will be administered to patients: EQ5D Questionnaire.

A sample of the EQ5D questionnaire is provided in Annex (Annex 6).

9.1.3 V2: Follow-up (up to 6 months post-enrolment) +/- 1 month

No visits are mandated or prescheduled as a part of the study. Follow-up information will be collected at the visit scheduled around 6-month post-prescription of Degarelix as a part of routine care. The data to be collected at the follow-up visit include AEs and other clinical outcomes, including all outcomes of interest, as follows: previous and concomitant treatments, changes in clinical examinations depending on the evaluated patient comorbidities, information on PCa (TNM classification, PSA and testosterone), smoking habits and alcohol consumption, evaluation of all data for each risk factor information towards with cardiovascular, metabolic, osteoporotic, geriatric comorbidities and mood and sexual disorders and changes in concomitant treatments.

Blood tests could be performed to evaluate the risk of comorbidities after 6 months of follow-up. All results from these laboratory tests will be collected by the Investigator in the eCRF.

At the time of the follow-up visit, the patient will be also asked to complete one questionnaire for QoL assessment: EQ5D questionnaire.

All serious adverse events (SAEs) and non-serious suspected adverse drug reaction (ADR) must be reported immediately to the Pharmacovigilance Ferring SAS by the investigator. Modalities of SAE/non serious ADR reporting are provided in Section 11.2.3.

9.1.4 Study Discontinuation

Patients withdrawing from the study before study end, lost to follow-up, change medical teams, or die will be documented as having early study withdrawal in the eCRF.

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

9.2 Setting

9.2.1 Inclusion criteria

Only patients who meet all the following inclusion criteria will be considered for inclusion in the study:

- Male aged 18 years or older
- Diagnosed with hormone dependant advanced prostate cancer PCa
- Patient having received an antagonist of GnRH Degarelix prescription
- Agreeing to and capable of completing in French during the visits all questionnaires on the impact of their illness and treatment
- Patients having received oral and written study information, agreeing to the use of his anonymized data, and having signed a written Informed Consent Form.

9.2.2 Exclusion criteria

Patients will not be included in the study if they meet at least one of the following exclusion criteria:

- Patient included in an interventional study assessing treatment for PCa,
- Patient presenting hypersensitivity to Degarelix or one of its excipients,
- Patient treated by other hormonotherapy

NB: ***it is important that patients are naive of hormone therapy to have objective epidemiological data of different comorbidities, including cardiovascular comorbidities.***

9.2.3 Withdrawal criteria

Patients may withdraw consent at any time without any prejudice.

Possible reasons for study discontinuations will be as follows:

- Patients not fulfilling the inclusion/exclusion criteria,
- Safety concerns requiring discontinuation from the study,
- Lost-to follow up,
- Patient's decision,

- Investigator's decision.

If a patient is withdrawn prior completion of the study or follow-up period, any reason for withdrawal will be documented in the database and the case report form (CRF), when 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 or guardian and no additional information will be entered in the study database.

9.3 Variables

Recruited patients will be followed up for 6 months (±1 month) after treatment initiation.

A total of 60 physicians should complete an eCRF for about 170 expected patients. Recruitment being competitive, physicians will be asked to include around 3 patients, with the potential to enroll more subjects upon sponsor approval, until the cohort of 170 patients has been obtained.

In addition, one validated QoL patient Questionnaire (EQ5D) will be filled in by patients at inclusion and at 6-month consultation.

The objectives will be evaluated using data entered in the electronic case report form (eCRF) and collected from the eCRF provided to physicians (for clinical data) and patients questionnaire (for QoL data) when available, given the non-interventional nature of the study.

OBJECTIVES :

Primary objective :

To describe the prevalence of the cardiovascular comorbidities, at the initiation of Degarelix, in PCa patients.

Secondary objectives :

1- To describe, at the initiation of Degarelix, the real-life prevalence of metabolic, osteoporotic comorbidities, mood and sexual disorders as well as the geriatric comorbidities in elderly patients (geriatric oncology) in PCa patients.

2- To describe patient characteristics at the time Degarelix is initiated.

3- To evaluate real-life prevalence of the comorbidities after 6 months of follow-up.

4- To describe the therapeutic management of PCa patients receiving Dégarélix, in order to provide real-life data of the impact of hormone treatment after 6 months.

5- To evaluate compliance with recommendations made by the CCAFU through the use of practical tools made available to the patient and his treating physician.

6- To describe the QoL of PCa patients receiving androgenic suppression hormone therapy, at inclusion and after 6 months of follow-up, and to compare QoL in terms of the presence or not of comorbidities.

7- To evaluate tolerance in PCa patients receiving Degarelix hormone therapy using real-life data from all AE over the 6-month period (data collection for comorbidities).

ENDPOINTS :

Primary endpoint :

A patient will be considered to have cardiovascular comorbidities if he has a history of at least one cardiovascular illness and/or at least three cardiovascular risk factors.

The following data will be collected :

- *Clinical examination (weight, height, BMI, waist circumference)*
- *History of cardio-neuro-vascular disease according to International Classification of Diseases, Tenth Revision [ICD-10]: number of cardiovascular disease among cerebrovascular accident or stroke [neurologist-certified], myocardial ischemia or infarction, coronary artery disease [cardiologist-certified], angina pectoris, heart failure [cardiologist-certified], peripheral artery disease, arrhythmia, etc.,*
- *Number of cardiovascular comorbidities factors (recommendations published by the Cancer Committee of the French Urology Association (CCAFU) in 2013 and 2016,*
- *Current medications (cardiac [angina, heart failure, etc.]),*
- *Clinical examination (systolic/diastolic blood pressure),*
- *Implementation of a cardiologist assessment.*

Secondary endpoints :

The endpoints for each secondary objectives are :

1- To describe the real life prevalence of comorbidities :

For metabolic comorbidities:

A patient will be considered to have metabolic comorbidities if he has a history of at least one metabolic disease (diabetes, lipid disorders or metabolic syndrome).

The following data will be collected :
lipid disorders , and/or diabetic, lipid profile (total cholesterol, triglycerides [TG], High Density Lipoprotein [HDL] - Low Density Lipoprotein [LDL]) and glycemic blood tests, clinical examination (BMI, waist circumference), metabolic syndrome, dietary/lifestyle measures (in place or to be implemented), and implementation of an endocrinologist assessment.

For osteoporotic comorbidities:

A patient will be considered to be with osteoporotic comorbidities if he presents a more than 20% risk of major fracture at 10 years, and/or a more than 3% risk of hip fracture at 10 years and/or a T-score < -2.

The following data will be collected :
Number of osteoporosis risk factors, history of falls, blood tests (creatinine, vitamin D) within normal ranges, full calcium/phosphorus blood tests (yes/no), evaluation of the risk of fracture with the FRAX score, osteodensitometry (bone mineral density), and evaluation of T-scores, prescription of daily vitamin D, and implementation of a rheumatologist assessment.

For elderly patients:

A patient will be considered to be with geriatric comorbidities if he is more than 70 years old and has a G8 score ≤ 14.

The following data will be collected :
Onco G8 questionnaire (score) and implementation of a geriatric and/or onco-geriatric specialist assessment.

For mood disorders:

Patient will be considered to be with depression comorbidities if his mini-GDS score is ≥ 1.

The following data will be collected :
Mini-Geriatric Depression Scale (mini-GDS) (score), patient concerns, and implementation of a psychiatrist or general physician assessment.

For sexual disorders:

Patient will be considered to be with sexual disorder comorbidities if he has erectile dysfunction, and/or ejaculation dysfunction, and/or pain or discomfort, and/or concerns over his desire or sex life.

The following data will be collected :
Erection or ejaculation dysfunction, pain or discomfort, concerns over desire or sex life, satisfaction with sex life (yes/no), sexual activity, Tessler, DAN-PSS, UROLIFE questionnaires, and implementation of a sexologist assessment.

2- To describe patient characteristics :
   - Patient demographic data
   - Medical and family history
   - Blood tests
   - Cancer diagnosis
   - Tumour stage
   - PSA levels
   - Testosterone levels
   - Concomitant medications

The following data will be collected :
- *Patient initials - Date of inclusion visit*

- *Verification of provision of Patient Information Sheet/Informed consent*
- *Patient demographic data: Date of birth, professional status, marital status*
- *Cigarette and alcohol consumption*
- *Medical history and Family history of cancer*
- *Hemoglobinemia*
- *Date of cancer diagnosis (biopsy)*
- *Biopsy: sites, number of samples*
- *Tumour stage at diagnosis (Tumor Node Metastasis staging system [TNM] classification) and prognostic factors (Gleason score)*
- *Prostate-specific Antigen (PSA) (ng/mL) and testosterone (ng/mL) levels*
- *Dose and duration of prior and ongoing treatments for PCa*
- *Drug class and duration of concomitant medications excluding PCa treatments (indication)*
- *Digital rectal examination (Yes/No)*
- *CT scan (Yes/No and reason)*
- *Magnetic resonance imaging (MRI): (Yes/No and reason); extraprostatic spread (Yes/No)*
- *C-choline PET/CT scan (Yes/No)*

3- To evaluate real-life prevalence of the comorbidities after 6 months of follow-up :

Modification of the comorbidities after 6 months (cardiac, metabolic, osteoporotic, geriatric, mood and sexual disorders).

The following data will be collected :

- *For cardiac comorbidities: changes in cardiovascular risk factors or cardiac concomitant medications, major cardiovascular events, changes in clinical examinations (systolic/diastolic blood pressure), follow-up by a cardiologist.*
- *For metabolic comorbidities: new lipid or glycemic abnormalities, changes concomitant medications, changes in clinical examinations (body mass index [BMI], waist, circumference), occurrence of metabolic syndrome, diabetes or lipid disorders, occurrence or continuation of poor dietary/lifestyle measures, follow-up by an endocrinologist.*
- *For osteoporotic comorbidities: change in the number of osteoporosis risk factors, falls events, osteoporotic events, blood tests (creatinine, vitamin D) within normal ranges, change in the risk of fracture with the FRAX® score, change in the prescription of daily vitamin D intake and/or supplementation, follow-up by a rheumatologist.*
- *For elderly patients (≥ 70 years): falls and lost autonomy assessment, follow-up by a geriatric and/or an onco-geriatric specialist.*
- *For mood disorders: mini-GDS (score), patient concerns, follow-up by a psychiatrist or a general physician.*
- *For sexual disorders: changes in erection or ejaculation dysfunction or in pain or discomfort, concerns over desire or sex life, change in Tessler, DAN-PSS, UROLIFE scores, follow-up by a sexologist.*

4- To describe the therapeutic management :
   - Tumor evolution : TNM
   - Biological evolution : PSA, Testosterone levels
   - All treatments for PCa over the 6-months period

The following data will be collected :

- *Visit date*
- *Cigarette and alcohol consumption*
- *PSA (ng/mL) and testosterone (ng/mL) data after 3 and 6 months*
- *TNM*
- *Extraprostatic spread (Yes/No)*
- *All treatments for PCa over the 6-months period (modifications to ongoing treatments, dose, treatment duration)*

5- To evaluate compliance with recommendations :

Percentage of patients whom benefits of the practice tools.

6- To describe the QoL of PCa patients :

QoL evolution during 6 months treatment.

The following data will be collected :

EQ5D at inclusion and after 6 months treatment

7- To evaluate tolerance :

Percentage of patients with at least one adverse event and adverse events description.

The following data will be collected :

All AE collected during the study period.

9.4 Data Sources

As a non-interventional study, all data will be collected during routine follow-up visits scheduled by physicians in clinical practice. Only data available in patients' medical files and other items that are evaluated as part of routine disease management will be collected.

9.5 Study Size

It is planned that 170 patients fulfilling the inclusion criteria will be consecutively included by participating physicians over a 12-month period.

It is planned that 170 patients fulfilling the inclusion criteria will be consecutively included by participating physicians over a 12-month period.

Sample size determination:

The primary objective of the study is to estimate prevalence of cardiovascular comorbidities.

The 95% confidence interval (95% CI) was used to justify the number of required patients. According to the literature (Leclercq C, 2012; Albrand G, 2012; Fremont P, 2012; Colson MH, 2012; O'Farrell S, 2015), the prevalence of cardiovascular comorbidities (at least one prior event) is estimated from 15% to 25%.

According to these hypotheses, 170 PCa patients eligible to receive androgenic suppression hormone therapy are required for a true prevalence of 20% and a Standard Error of the prevalence estimate of 3%.

With 170 patients, width of the corresponding 95% Confidence Interval is then approximately 12% which is deemed sufficient for the trials purpose. The 95% two-sided CI is expected to be [8%; 32%].

9.6 Data Management

9.6.1 Electronic CRF and patient questionnaire

Electronic CRF (eCRF)

In the study an eCRF 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.

An eCRF completion guideline will be prepared and provided to investigators. A training session using validated documents will be organised in each centre before the beginning of the study.

AEs and terms of concomitant medications will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Only the investigator will be allowed to fill in the eCRF or to make corrections. He will approve/authorize the eCRF entries for each patient with an electronic signature which is equivalent to a handwritten signature. Data should be entered into the system within 7 days after the patient has attended a visit.

The eCRF 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 investigator will also receive a copy of the trial site's final and locked data (including audit trail, electronic signature and queries) as write-protected PDF-files produced by the independent third party CRO.

Patient questionnaire

The capture of patient questionnaires, coding and control data to the operating results of the study will be performed by the CRO in charge of the conduct of the study, [redacted], under the supervision of the Sponsor, Ferring SAS.

Patients will be asked to complete the EQ5D questionnaire for QoL assessment completely and legibly with a black ballpoint pen.

Once completed, the "patient" questionnaire should be sent by pre-paid envelope to the CRO, [redacted].

The data from the "Patient" questionnaire will be entered by the data management department of the CRO. A duplicate data entry will be done.

All anonymous questionnaire data will be stored in a computer database under the control of the Data Manager of the Company in charge of logistics and data management.

The gathering of two databases generated by entering the eCRF and paper patient questionnaire will result in the creation of a single database.

9.6.2 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 Data Manager will write the different versions of the Data Validation Plan which describes all the consistency test specifications, and the different versions of the Self Evident Corrections Specifications. When the Sponsor approves these documents, the Data Manager will program and validate consistency tests and listings.

The DCFs (Data Clarification Forms) and the SECs (Self Evident Corrections) will be automatically generated and tracked with the software. Queries will be issued directly via the eCRF.

Before the database lock, a Quality Control of data for patient questionnaires will be performed on $\sqrt{n} + 1$ CRFs, according to the Quality Control plan: printed SAS data versus CRF data will be confronted. The Data Manager will write a Quality Control Report.

Before the study review, the Data Manager will perform the Data Review Plan which describes the different deviation listings. This document must be approved by the Sponsor.

At the end of the study, a request for authorization for database lock will be sent to the Sponsor. Once the database lock is made, the final report of data management and the database lock certificate will be sent to the Sponsor.

A complete, remapped, version of the database will be transferred to the Sponsor on an ongoing basis.

9.7 Data Analysis

9.7.1 Software

The statistical analysis will be performed by the CRO, [redacted] under the responsibility of the Sponsor, using SAS® software (SAS Institute, NC, Cary, United-Kingdom) version 9.4 or later. A statistical analysis plan will be written in order to detail statistical analyses and will be finalized prior to the database-lock. This document must be approved by Ferring SAS.

9.7.2 Populations

The number of non-included patient (from the register) will be described. On the available criteria, a comparison between subjects who have agreed with those who refused, will be done. An individual data listing of non-inclusion reason will be done.

The number of all included patients will be described.

The population of evaluable patients which consists of all included patients for whom an eCRF is correctly completed and considered assessable will be provided.

The number of patients having completed the QoL questionnaire will be presented at inclusion and at the 6-month follow-up.

The Safety Set is composed of all subjects having received at least one dose of Degarelix. This set will be used to perform analysis of Safety.

The population of participating physicians is defined as all physicians having signed financial agreement and with an initiation visit by phone performed by a CRA.

The number of active physicians will also be given. The population of active physicians is defined as all physicians who will fill in at least one eCRF.

9.7.3 Planned Analyses

The collected parameters will be described on the population of evaluable patients, and/or on the data provided by patient questionnaire for QoL assessment.

Analyses may be performed by sub-groups by type of prescriber: private or public urologist or by type of patient depending on the length of PCa diagnosis.

The expression of the distribution of each of the variables depended on their nature:

- Continuous variables: their distribution will be expressed by their median and quartiles (for non-Gaussian variables), or mean (m), standard deviation (SD), range with minimum and maximum, missing data,
- Qualitative variables: their distribution will be expressed by the frequency of each modality and the number of missing data.

9.7.3.1 Analyses of the primary objective

For the primary analysis, the prevalence of cardiovascular comorbidities at the prescription will be described along with the 95% CI.

The prevalence of cardiovascular comorbidities is defined by a history of at least one cardiovascular illness and/or at least three cardiovascular risk factors.

9.7.3.2 Analyses of the secondary objectives

1. To describe, at the initiation of Degarelix, the real-life prevalence of metabolic, osteoporotic comorbidities, mood and sexual disorders as well as the geriatric comorbidities in elderly patients (geriatric oncology) in PCa patients.

   The prevalence of osteoporotic comorbidities, and metabolic comorbidities, of mood and sexual disorders, as well as the geriatric comorbidities in elderly patients, among PCa patients receiving Degarelix will be described along with the 95% CI (see section 9.3 – secondary objectives for the comorbidities prevalence definition).

2. To describe patient characteristics at the time Degarelix is initiated. Analyses of the data above-described in Section 9.3 are descriptive.

3. To evaluate real-life prevalence of comorbidities after 6 months of follow-up.

   The prevalence of cardiac, metabolic, osteoporotic, and geriatric comorbidities, and mood and sexual disorders, among PCa patients receiving Degarelix will be described along with the 95% CI. Over a 6-month period prevalence will increase by newly incident cases. Prevalence rates before and after Degarelix initiation will be compared with the methodology described in Matthew Smith et al. Gonadotropin-Releasing Hormone Blockers and Cardiovascular Disease Risk: Analysis of Prospective Clinical Trials of Degarelix (Journal of urology 186(5):1835-42 · September 2011).
   CVD event rate before and after Degarelix treatment was investigated by Kaplan-Meier plots of time to events setting 6 months before treatment initiation as baseline. A change of hazards from the pre- to the post-treatment period was analysed by the Likelihood Ratio test ($\chi 2$, df=1) associated with the two-parametric exponential model as described in Kim DY, Woodroofe M, Wu Y. Testing for a change in the Hazard Rate with Staggered Entry (Communications in Statistics - Theory and Methods. 2004;33:2041–2058). The corresponding hazard ratios (HR) and their 95% CI were inferred using the delta-method and standard maximum-likelihood theory. Kaplan-Meier plots of time to first new CVD event in the total population, in subjects with no CVD and in subjects with established CVD starting 6 months prior Degarelix treatment will be provided.

4. To describe the therapeutic management of PCa patients receiving hormone therapy, in order to provide real-life data of the impact of hormone treatment after 6 months. Analyses of collected data described in Section 9.3 will be descriptive.

5. To evaluate compliance with recommendations made by the CCAFU tools made available to the patient and his treating physician. The evaluation will focus on compliance with the recommendations of CCAFU through the research of comorbidities (cardiac, metabolic, osteoporotic, mini-GDS, sexual and Onco G8 questionnaires) according to current data.

6. To describe the QoL of PCa patients receiving androgenic suppression hormone therapy, at inclusion and after 6 months of follow-up, and to compare QoL in terms of the presence or not of comorbidities described in the primary and secondary objectives.

   Evolution of QoL of PCa, patients characteristic and care for patient under Degarelix treatment after 6 months: all comorbidities (cardiac, metabolic, osteoporotic, geriatric, mood disorder and sexual disorder) will be compared between baseline and 6 months.

7. To evaluate tolerance in PCa patients receiving Degarelix hormone therapy using real-life data from all AE over the 6-month period (data collection for comorbidities), (see Section 9.7.3.3).

The statistical tests for paired sample used to compare those comorbidities will depend on analyses, type and distribution.

The normal distribution for continuous variables will be checked prior to analysis by the Shapiro-Wilks test: T-test for paired data or Wilcoxon matched-pairs signed-ranks test will be used in function of the distribution.

In case of categorical variables, Cochran Q or Mac Nemar tests will be used.

A level of significance at 0.05 in two-sided test will be defined.

9.7.3.3 Safety analysis

The safety analyses will be carried out on the safety population.

The number of AEs and the proportion of patients experiencing at least one AE, serious AE, severe AE, possibly related AE, AE causing premature discontinuation, AE leading to death will be provided.

AEs will be presented by system organ class (SOC) and preferred term (PT).

Any AE having been reported during the study will be recorded in safety database and request will be available by subject number, indicating its nature, its intensity, its start and end, duration, its outcome, the use of corrective treatment and its possible link with Degarelix.

9.7.3.4 Missing data

Missing data will be not taken into account for analysis. Percentage will be calculated on evaluable numbers.

9.8 Quality Control

The preparation, implementation and monitoring of the study, and the capture, coding and control data to the operating results of the study will be carried out in accordance with internal procedures of Ferring SAS and standard operating procedures in force at [redacted] (ISO 9001 certified for its entire clinical research activity) and in accordance with standards (Good Pharmacoepidemiology Practices) and laws under the control of the Assurance Quality Manager.

9.8.1 Periodic Monitoring

A central monitoring will be conducted with health professionals participating in the study by clinical research associates (CRA) of the CRO in charge of the study, [redacted].

Reminders will be conducted regularly in case of inconsistent or missing information through e-mail and telephone contacts.

Throughout the monitoring period, receiving documents and data quality will be regularly monitored by the staff of the CRO with a regular review (weekly) including the number of selected and participating physicians, the number of "patient" questionnaires received, the number of eCRF completed.

Phone support available by hotline will also be established at the disposal of participating physicians.

No specific procedure for the patients lost will be required.

No on-sites monitoring visits will be planned.

However, to ensure adherence to the Protocol and applicable regulatory requirements, completeness, accuracy and verifiability of eCRF entries will be carried out at distance by the CRA. If deemed needed, some sites might be visited. The investigator 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 investigator will co-operate with the Monitor to ensure that any discrepancies that may be identified are resolved. The investigator is expected to be able to meet the Monitor during these visits.

9.8.2 Audit/Inspection

Similarly, audits/inspections may be conducted during the study and/or at the end of the study by representatives of the Sponsor or the appropriate regulatory authorities. In this later case, the Sponsor will be informed immediately. Moreover, participating physicians in the study undertake to be available for providing any additional information, and will facilitate access to documents needed for the study.

9.9 Limitations of the Research Methods

No randomization for treatment assignment versus a control group will be performed as a PASS study has been chosen to be carried out. This study design has been adopted to collect further information on the safety of Degarelix once it is on the market, and to assess the effectiveness of risk-management measures taken in clinical practice.

There can be a selection bias, as the sample of participating physicians is not randomly selected, and might not be representative of all professionals working in France. The method of physician selection will not ensure sample representativeness, and furthermore physicians can refuse to participate in the study. Sample representativeness will thus be determined by comparing the initial sample of the Sponsor's national database of sites with the sample of active sites. All results should be interpreted cautiously.

To minimize possible bias of patient recruitment, physicians will be asked to include all consecutively patients who meet the inclusion criteria and agree to participate in the study. A register (with anonymous patient data) will be completed by physicians for all patients (included or not) who meet the inclusion criteria. For patients not included, the reason of non-inclusion will be collected in the register.

In addition, as part of an observational study with prospective cohort study evaluated over a 6-months period, it is important to take into account the handling of missing data for the primary endpoint when considering the accuracy of estimation and relevance of the study results. Nonetheless, because the primary objective is evaluated at baseline, this bias should be reduced.

9.10 Other aspects

None.

10 PROTECTION OF HUMAN SUBJECTS

10.1 Independent Ethics Committee (IEC)

The study documents (protocol, Patient Information Sheet and Informed Consent Form) will be submitted to an IEC for information.

10.2 Patient Information and Consent

After the investigator has made the decision to treat the patient with Degarelix, the investigator will obtain a freely given written consent from each patient after an appropriate explanation of the aims and procedures of the study. 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 is exposed to any study-related procedure, including screening tests for eligibility.

The investigator 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 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.

A sample of the patient information and consent form is provided in Annex (Annex 3).

10.3 Confidentiality of Patient Data

The investigator will ensure that the confidentiality of the patients' data will be preserved. In the eCRF or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by an identification system, which consists of an assigned number in the 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 investigator in strict confidence.

10.4 Compliance Reference Documents

The study will be conducted in compliance with the Appendix 1 of the EMA Guidelines on good pharmacovigilance practices (GVP) on Post-authorisation studies (Module VIII), Guidance in the ENCePP Guide for Methodological Standards for further details on PASS study design, ethical principles defined in the Helsinki Declaration, Guidelines for Good Pharmacoepidemiology Practice (GPP; Initially Issued: 1996, Revision 1: August 2004, Revision 2. April 2007, updated on June, 2015) which includes an obligation of reporting by any physician who suspects a serious or unexpected adverse drug reaction whether or not he has prescribed the medication, French Public Health Code and other national laws in Force in France where the study takes place that shall constitute the main reference guidelines for ethical and regulatory conduct.

The study will also comply with the Data Protection Act 78-17 of 6 January 1978, modified by the Law No. 94-548 of 1 July 1994, completed by an implementing decree on 9 May 1995.

In this context, a copy of the study protocol and a sample of the patient questionnaire and eCRF intended for physicians will be submitted to the Consultative Committee for the data processing in health research (CCTIRS) for advice and the French Data Protection Agency (CNIL) for approval prior to the study start.

In addition, a copy of the study protocol and financial contracts related to the study will be submitted for review to the French National Council of the College of Physicians (CNOM) in accordance with the Article L. 4113-6 of the Public Health Code.

Each investigator will receive three copies of the financial convention of which one will have to be sent by him to the County Council of the Order of Physicians of which he depends (Article L.4113-9 of the French Public Health Code).

In accordance with the Law n°2011-2012 dated from December 29th, 2011, on the strengthening of drug and health products safety and the Decree n° 2013-414 dated from May 21st, 2013 on the transparency of the remuneration granted by companies producing or marketing products for health or cosmetic purpose for humans, the Sponsor is required to publish on a public website and submit to the CNOM for publication, the remunerations (kind or cash) granted to health professionals or associations representing them and the existence of agreements that the Sponsor concludes with the latter within 15 days following the agreement signing.

10.5 Study Documentation

- **Site File**

The investigator 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 Guidelines for Good Pharmacoepidemiology Practices (GPP) filing standard. The study documentation including all the relevant correspondence should be kept by the investigator for at least 5 years after the completion of the Non-Interventional Study Report, if no further instructions are given by the Sponsor.

The investigator is responsible for the completion and maintenance of the confidential patient identification code which provides the sole link between named patient source records and anonymous eCRF data for the Sponsor. The investigator 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 Non-Interventional Study Report, if no further instructions are given by the Sponsor.

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

- **Study Master File**

The study documents will be archived by Ferring in accordance with its procedures and applicable regulatory requirements.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS

11.1 Adverse Events

11.1.1 Definitions

Adverse Event (AE)

An AE is any untoward medical occurrence in 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 AEs anticipated based on the pharmacological effect of the medicinal product.

Serious AEs (SAEs)

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

- Results in death[1]
- Is life-threatening[2]
- Requires in-patient hospitalisation or prolongation of existing hospitalisation[3]
- Results in persistent or significant disability/incapacity[4]
- Is a congenital anomaly/birth defect[5]
- Is an important medical event[6]

To be noted that the special situation 'any suspected transmission of an infectious agent via a medicinal product' is also assessed as a serious adverse event.[7].

[1] 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.

[2] 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.

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

[4] Disability/incapacity means a substantial disruption of a person's ability to conduct normal life functions. In doubt, the decision should be left to medical judgment by the investigator.

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

[6] Important medical events are events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of important medical events include 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.

[7] 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 seriousness criteria should not be confused with the intensity of the event.

Special situations requiring pharmacovigilance notification
Any noxious and unintended reaction arising from the following special situations must be reported by the investigator immediately and within 24 hours from the date of the first awareness to the Pharmacovigilance Ferring SAS by completing and sending the Pharmacovigilance confidential form (Annex 4), using the contact details below :

Pharmacovigilance, Ferring SAS
E-mail: [redacted]

The special situations are :

- Any overdose of the medicinal product: administration of a quantity of the medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information.
- Any medication errors: any unintentional error made by a healthcare professional, a patient or a third party in the prescribing, dispensing, or administration of the medicinal product.
- Any abuse of the medicinal product: persistent or sporadic, intentional excessive use of the medicinal product which is accompanied by harmful physical or psychological effects.
- Any drug interaction involving the medicinal product.
- Professional exposure: exposure to the medicinal product, as a result of one's professional occupation.
- Any suspected transmission of any infectious agent via the administration of the medicinal product.
- Any off-label use: situations where the medicinal product is intentionally and inappropriately used for a medical purpose not in accordance with the authorized dose regimen, administration route, therapeutic indications or not following the terms of the marketing authorization.
- Lack of drug effect/drug ineffective : the drug was ineffective, did not work, or similar wording, or that the expected effect was not obtained.

11.2 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.
The investigator must record all AEs on the AE CRF module provided in each patient's 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].

11.2.1 Causal Relationship to Medicinal Product

The possibility of whether the medicinal product caused the AE must be classified as one of the following:

Reasonable possibility:

There is evidence or argument to suggest a causal relationship between the medicinal product and the AE. The AE may occur as part of the pharmacological action of the medicinal product or may be unpredictable in its occurrence.

Examples:

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

No reasonable possibility:

There is no reasonable evidence or argument to suggest a causal relationship between the medicinal product and the AE.

Examples:

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

11.2.2 Pregnancy and Pregnancy Outcome

A female partner of a male patient becomes pregnant during the study period, the pregnancy must be reported by the investigator immediately and within 24 hours from the date of the awareness to the Pharmacovigilance Ferring SAS by completing and sending the Pregnancy form.

The Pregnancy forms (Annex 5) are available in the investigator's file. The Pregnancy forms should be completed in accordance with the instructions provided on the form and sent to Ferring SAS Pharmacovigilance using the contact details below :

Pharmacovigilance, Ferring SAS
E-mail: [redacted]

The pregnancy outcome must also be reported by the investigator.

11.2.3 Collection and Recording of AEs and SAEs

All SAEs and non-serious suspected adverse drug reaction (ADR) must be reported immediately to the Pharmacovigilance Ferring SAS as soon as it becomes known to the investigator and not later than within 24 hours of their knowledge of the occurrence of a SAE.

SAE/non-serious suspected ADR must be reported to Ferring SAS via the pharmacovigilance confidential form.

The investigator is responsible for submitting the completed pharmacovigilance confidential form with the fullest possible details immediately and within 24 hours of his/her knowledge of the SAE/non-serious suspected ADR.

The pharmacovigilance confidential form is available in the investigator's file. The pharmacovigilance confidential form should be completed in accordance with the instructions provided on the form and sent to Ferring SAS Pharmacovigilance using the contact details below :

Pharmacovigilance, Ferring SAS

E-mail: [redacted]

Copies from eCRFs regarding demographics, AEs, medical history and concomitant medication is mandatory for initial reports and for follow-up reports if any changes have been made since the initial report.

Additional information relevant to the SAE such as hospital records, results from investigations, e.g. laboratory parameters (that are not already uploaded in the eCRF, invasive procedures, scans and x-rays, and autopsy results can be faxed or scanned and e-mailed to Ferring SAS Pharmacovigilance using the contact details in the section above. In any case this information must be supplied by the investigator upon request from Ferring. On any copies provided, such details such as subject's name, address, and hospital ID number should be concealed and instead subject number should be provided.

The investigator will supply Ferring with any additional requested information such as results of post-mortem examinations and hospital records.

11.2.4 Post-Study Safety Collection

If an investigator becomes aware of a 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.

11.2.5 Regulatory Reporting Responsibilities

AEs/SAEs will be reported to national 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.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 Observational Study Report

The data and information collected during this study will be reported in a Study Report prepared by the CRO, [redacted].

12.2 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 investigator and any other persons involved in the study will protect the confidentiality of this proprietary information belonging to Ferring.

12.3 Publication Policy

The results will be submitted for publication in a peer-reviewed journal.
The procedures for scientific result publication and authors involved in these publications and communications will be defined by the Sponsor which reserves the worldwide copyright of all important publications, including translations into other languages.
The Scientific Committee will take part in communicating the study results.

The Sponsor reserves the rights to:

- Use the study results for any regulatory procedure, on its own behalf or that of subsidiaries.
- Present the results in its medical information letter on drugs.
- Distribute reprints of the publications.

No one may use these rights without the prior written authorization of the Sponsor.

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List of annexes :

Annex 1 : List of Stand-alone documents
None.

Annex 2 : ENCePP Checklist for Study Protocols

Annex 3 : Patient information and consent form

Annex 4 : Pharmacovigilance confidential form « Formulaire confidentiel de pharmacovigilance »

Annex 5 : Pregnancy forms :

- « Formulaire de grossesse confidentiel antécédents et début de grossesse »
- « Formulaire de grossesse confidentiel déroulement et issue de grossesse »

Annex 6 : EQ-5D health questionnaire

Annex 7 : Register

Annex 1 : List of Stand-alone documents

None.

Annex 2 : ENCePP Checklist for Study Protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Observational prospective study describing the global patient care and follow-up of prostate cancer patients treated with Degarelix
DUO study (Dialogue in Uro-Oncology)

Study reference number:
000235

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	22
1.1.2 End of data collection[2]	☒	☐	☐	22
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	22
1.1.6 Final report of study results.	☒	☐	☐	22

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

ENCePP Checklist for Study Protocols (Revision 2)

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	23-25
2.1.2 The objective(s) of the study?	☒	☐	☐	24-25
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	30
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	25-27
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	31-35
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	38-39

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	30
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	28-31
4.2.2 Age and sex?	☒	☐	☐	31
4.2.3 Country of origin?	☒	☐	☐	25
4.2.4 Disease/indication?	☒	☐	☐	30
4.2.5 Co-morbidity?	☒	☐	☐	30
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	30

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☐	☒	

ENCePP Checklist for Study Protocols (Revision 2) 2

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	31-35/37-39
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	27

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	35-36
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	31-35
8.1.3 Covariates?	☒	☐	☐	31-35
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	31-35
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	31-35
8.2.3 Covariates? (e.g. age, sex, clinical and drug use				

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	31-35
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	35
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	42

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	35

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	37-39
10.3 Are descriptive analyses included?	☒	☐	☐	37-39
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	39
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	35-37
11.3 Are methods of quality assurance described?	☒	☐	☐	39-40
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	40
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	8-9

Comments:

ENCePP Checklist for Study Protocols (Revision 2) 4

Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	41-42
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	41-42
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	42
12.3 Does the protocol address other limitations?	☒	☐	☐	27

Comments:

Section 13: Ethical issues	Yes	No	N/A	Page Number(s)
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	42
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	43
13.3 Have data protection requirements been described?	☒	☐	☐	43

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Page Number(s)
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	22

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Page Number(s)
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	47
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	47

Comments:

Name of the main author of the protocol: ____Patin_____

Date: 27/06/2016

Signature: _____ [redacted] _____

ENCePP Checklist for Study Protocols (Revision 2) 5

Annex 3 : Patient information and consent form

Observational prospective study describing the global patient care and follow-up of prostate cancer patients treated with Degarelix
DUO study (Dialogue in Uro-Oncology)

Dear Sir,

You are going to start a treatment with Firmagon® (Degarelix) for your prostate cancer.
Your doctor currently participates in the DUO study, a non-interventional study, which is sponsored by Ferring SAS.
This document provides information about the purpose and nature of the study.
Please take time to read carefully this information sheet before taking any decision, and keep it with you in order to read it again during the study.
If there are points you do not understand or if you wish to obtain additional information on any aspect of the study, please contact your doctor.

What is the purpose of this study?

This is a non-interventional, national, longitudinal, multicenter, prospective cohort, post-authorization safety study.
That means that the prescription of Firmagon® will be freely decided and carried out by your doctor according to his/her opinion and current practice the day of the consultation.
The purpose of this study is to evaluate the prevalence of cardiovascular as well as osteoporotic, metabolic comorbidities, mood and sexual disorders and geriatric comorbidities among adult prostate cancer patients receiving Firmagon® (Degarelix) before treatment and after 6 ± 1 months of follow-up.
This study also aims to provide real-life data on your care and quality of life.

The DUO study will therefore be performed to obtain further information on the safety of Firmagon®, and better identify possible risk factors associated with your treatment.

Who can be involved in this study?

The study will be conducted only in France, and will be proposed to adult patients with advanced prostate cancer. Approximately 170 patients are expected to take part in this study.

What are the main characteristics of this product?

Firmagon® (Degarelix) is a hormone therapy and a gonadotropin-releasing hormone antagonist of androgen-dependent advanced prostate cancer. It has a direct mechanism of action that blocks the action of gonadotropin-releasing hormone on the pituitary limiting the testosterone secretion.

What do I have to do?

The DUO study is an observational study. This means that your medical care and treatment will not be modified because of your participation to this study (no additional examination, procedure, drugs or intervention will be imposed or proposed to you by the fact of participating in this study).

During your consultation, you will receive information verbally and in writing on this study. Your doctor will check your inclusion criteria for participation in the study and propose you to participate in the study.

If you decide to participate, your follow-up duration will begin from the prescription and initiation of your treatment with Firmagon®. This follow-up will be about 6 months. Your doctor will complete a questionnaire with information about yourself, the consultation day, and 6 ± 1 months after this consultation.

If you decide to take part in this study, the following medical data, which are already routinely collected by your doctor, will be entered by him/her in an electronic case report form, which is specific to this study: demographic data, medical and family history, comorbidities, smoking and alcohol consumption, previous and concomitant treatments, data on treatment with Firmagon® (used in accordance with the product leaflet), laboratory testings, radiographic assessments, and health status. In addition, you will be asked to answer some questions on two questionnaires concerning your quality of life.
Your participation in this study will consist only in the collection of these information by your doctor; you will not be asked for any particular effort due to the study.
Data collected in the case report form of the study will be the same as those collected during the routine follow-up visit scheduled by your doctor.

Do I have to take part?

It is up to you to decide whether or not you will take part in this study. Your participation is voluntary. You are free to refuse to participate or to withdraw from the study at any time. You are not required to explain your reasons for withdrawing. If you withdraw, you will not suffer from any prejudice regarding your medical care, and your refusal to participate will not affect your relationship with your doctor.

After agreeing to participate in the study, can I change my mind?

You can always withdraw your consent at any time without having to justify yourself and without affecting the quality of your care and monitoring.
In this case, simply inform your doctor about your withdrawal decision. If you withdraw your participation, you can object to your data being used. You can also enable Ferring to use the data collected up to the time of your withdrawal from the study.

What side effects related to Firmagon® can be expected?

Firmagon® is generally well tolerated. However, bothersome effects may occur in some cases. The most frequently reported side effects are physiological consequence of castration including hot flashes and weight gain (reported in 25 % and 7% of patients treated for one year) and injection site reactions. If you think that you present a side effect, do not hesitate to contact your doctor who follows your treatment in the context of the study.

Will my taking part in this study be kept confidential?

All personal information (data) will be managed and analyzed with the greatest confidentiality. Your data will be collected in an anonymous manner. A unique code number will be attributed to the data. All study documents will be identified using a unique number, without mentioning your first name and family name. Only your doctor has the mapping between your identifier code and your identity.
In case of a quality control, Ferring SAS representatives or competent authorities, could verify, by checking your medical records, the data collected by your doctor in the DUO study questionnaires during or after the study.
According to the current legislation, these people are covered by the obligation of professional secrecy and your medical record will remain strictly confidential.

Has the study been approved?

Study data will be electronically processed according to the amended Act No. 78-17 of 6 January 1978, modified by the Law dated August 6, 2004, regarding information technology, files and freedoms.
Before its implementation, the DUO study has received favorable opinion from the Consulting Committee for the processing of data related to research in the health field (Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé - CCTIRS), and authorization from the French Data Protection Agency (Commission Nationale de l'Informatique et des Libertés, CNIL).
Therefore, you have the right to access and correct all personal data. You also have the right to oppose the transmission of your data protected by professional secrecy. That may be used as part of the study.
The doctor in charge of the study, who is the only one to know your identity, may apply those rights. You can also reach directly, or through the doctor of your choice, for all your medical data according to the article L 1111-7 of the French Public Health Code.
Once the study is completed, you can ask for the results to your doctor.

Who do I call to have more information?

Please contact your doctor (name: _____
Phone number: _____) at all times if you have any questions or concerns about this study or if you think a side effect is appearing.

Thank you in advance for your participation in the DUO study.

INFORMED CONSENT FORM

Center number: _____ subject inclusion number: _____

Dr._____informed me about the nature and the purpose of this study.

He/she also specified it will be conducted by Ferring laboratory.

I know I can withdraw from this study at any time without prejudice.

I agree to grant to Ferring authorized representatives as well as regulatory authorities, direct access to my original medical record in order for them to review and process my personal data for the purpose of this study.

I read and I understand the note "Patient Information", final version of 20/09/2016 as well as the "Informed Consent Form" final version of 20/09/2016.

I received detailed information regarding the study and I agree to participate. I understand that my participation in the study is voluntary.

I also know that personal data will be kept confidential and that my identity will never be revealed in any publication resulting from this study.

I agree that my personal data collected during this study can be processed electronically by Ferring authorized representatives for the sole purpose of the conduct of this study.

I am fully aware that I can exercise, at any time, my right of access to and rectification of all of my personal data, as defined by Act No. 78-17 of 6 January 1978, modified by the Law dated August 6, 2004, regarding information technology, files and freedoms, by contacting directly the doctor who follows me during this study. I understand I have the right to oppose the processing and transmission of my data protected by professional secrecy.

Name of the patient: _____
(In capitals or block letters)
Date* Signature

The patient will receive the information note and informed consent form dated and signed.

As Investigator, I state that the patient received adequate information regarding the study and that I obtained his informed consent.

Name of the Investigator: _____
(In capitals or block letters)
Date* Signature
* Personally dated

Annex 4: Pharmacovigilance confidential form « Formulaire confidentiel de pharmacovigilance »

FORMULAIRE CONFIDENTIEL DE PHARMACOVIGILANCE
(réservé aux professionnels de santé)

FERRING
PRODUITS PHARMACEUTIQUES

Etude n° : _____ Observatoire : _____ Numéro de Centre : ⌊_⌊_⌊_⌋ Numéro de Patient : ⌊_⌊_⌋	**N° FERRING S.A.S. :** **Type de rapport :** ☐ Initial ☐ Suivi n°_____

COORDONNÉES DU NOTIFICATEUR	**CRITÈRES DE GRAVITÉ**	
Nom – Prénom – Spécialité :	**Grave :** ☐ **Oui** ☐ **Non**	**Si grave, merci de spécifier le critère:** ☐ Décès Date :____/____/_____ ☐ Menace vitale immédiate ☐ Incapacité ou invalidité importante ou durable ☐ Hospitalisation ou prolongation d'hospitalisation ☐ Anomalie ou malformation congénitale ☐ Evènement indésirable médicalement grave
Adresse - Téléphone :		
Date de notification : _____/_____/_____		
Tampon et signature :		

INFORMATIONS SUR LE PATIENT	**GROSSESSE / ALLAITEMENT / EXPOSITION PATERNELLE**
Deux premières lettres du nom de famille: _____ Sexe: ☐ M ☐ F Date de naissance (JJMMAAAA) : _____/_____/_____ Age: _____ Taille : _____ cm Poids : _____ kg	**Grossesse :** ☐ Oui ☐ Non **Si oui, merci de spécifier l'âge gestationnel et compléter le formulaire de grossesse :** _____ Semaines et _____ Jours **Allaitement :** ☐ Oui ☐ Non **Exposition paternelle :** ☐ Oui ☐ Non
Antécédents médicaux et familiaux :	

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FORMULAIRE CONFIDENTIEL DE PHARMACOVIGILANCE
(réservé aux professionnels de santé)

FERRING
PRODUITS PHARMACEUTIQUES

ÉVÈNEMENTS INDÉSIRABLES

Grave		Réaction	Durée de l'évènement		
Oui	Non	De préférence un diagnostic, si indisponible, merci de fournir tous les symptômes	Date de début (JJMMAAAA)	Date de fin (JJMMAAAA)	En cours
☐	☐				☐
☐	☐				☐
☐	☐				☐
☐	☐				☐

MÉDICAMENT FERRING ADMINISTRÉ AU COURS DE L'ÉTUDE

Nom commercial : _____ Numéro de lot : _____ Date d'expiration : _____

Dosage			Durée du traitement			Lien de causalité		Indication
Forme	Voie d'administration	Posologie quotidienne	Date de début (JJMMAAAA)	Date de fin (JJMMAAAA)	En cours	Relié	Non relié	
					☐	☐	☐	

MESURES PRISES *(en réponse à l'évènement indésirable)*

☐ Aucune / posologie inchangée ☐ Augmentation de la posologie ☐ Diminution de la posologie
☐ Interruption temporaire du médicament ☐ Interruption définitive du médicament ☐ Traitement ou mesures correctrices (préciser) :

ÉVOLUTION *(au moment de la notification)*	*L'évènement indésirable a-t-il disparu à l'arrêt du médicament ?*	*L'évènement indésirable est-il réapparu après réintroduction du médicament ?*
☐ Récupération complète Date de guérison (JJMMAAAA) : _____/_____/_____ ☐ Récupération avec séquelles ☐ Amélioration ☐ Anomalie toujours présente inchangée ☐ Anomalie s'aggravant ☐ Décès dû à l'évènement Date du décès (JJMMAAAA) : _____/_____/_____ (joindre le compte-rendu d'autopsie) ☐ Inconnue	☐ Non	☐ Non
	☐ Oui	☐ Oui
	☐ Sans objet	☐ Sans objet

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FORMULAIRE CONFIDENTIEL DE PHARMACOVIGILANCE
(réservé aux professionnels de santé)

FERRING
PRODUITS PHARMACEUTIQUES

AUTRE(S) MÉDICAMENT(S) SUSPECTÉ(S)

☐ **AUCUN**

Médicament		Dosage			Durée du traitement		Lien de causalité		Indication
Nom commercial ou générique	Numéro de lot / date d'expiration	Forme	Voie d'administration	Posologie quotidienne	Date de début (JJMMAAAA)	Date de fin (JJMMAAAA)	Relié	Non relié	
							☐	☐	
							☐	☐	
							☐	☐	

TRAITEMENT(S) CONCOMITANT(S) *(exclus ceux utiliser pour traiter l'événement)*

☐ **AUCUN**

Médicament		Dosage			Durée du traitement		Indication
Nom commercial ou générique	Numéro de lot / date d'expiration	Forme	Voie d'administration	Posologie quotidienne	Date de début (JJMMAAAA)	Date de fin (JJMMAAAA)	

EXAMENS COMPLÉMENTAIRES *(si possible joindre un double des examens effectués – compte-rendu ...)*

Examens complémentaires	Date			Valeur	Date			Valeur	Date			Valeur
Intitulé	Jour	Mois	Année		Jour	Mois	Année		Jour	Mois	Année	

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FORMULAIRE CONFIDENTIEL DE PHARMACOVIGILANCE
(réservé aux professionnels de santé)

FERRING
PRODUITS PHARMACEUTIQUES

COMMENTAIRES : *Description de l'évènement indésirable (signes, symptômes, données significatives…)*

La maladie d'origine ou les maladies concomitantes ont-elles pu avoir un rôle dans l'apparition ou la survenue de ce(s) évènement(s) indésirable(s) : ☐ Oui ☐ Non

Si oui, merci de préciser : _____

_____

_____

« Vos données personnelles font l'objet d'un traitement par FERRING SAS destiné à gérer votre notification. Conformément à la loi « Informatique et libertés » du 6 janvier 1978 modifiée, vous disposez d'un droit d'accès et de rectification à vos données, que vous pouvez exercer auprès du Responsable Juridique par mail : service.juridique@ferring.com ou par courrier au 7, rue Jean-Baptiste Clément - 94250 GENTILLY. La pharmacovigilance étant une obligation légale de FERRING SAS, vous ne pouvez pas vous opposer au traitement de vos données. Nous vous prions de bien vouloir transmettre oralement à votre patient(e) les informations ci-dessus en lui précisant qu'il/elle peut exercer son droit d'accès et de rectification auprès de FERRING SAS par votre intermédiaire ».

A renvoyer au Laboratoire Ferring – Service de Pharmacovigilance – sous 24 h par e-mail : [redacted]

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Annex 5 : Pregnancy forms :

« Formulaire de grossesse confidentiel antécédents et début de grossesse »

MO-P-0004.04, Annexe 3
Version 4

FORMULAIRE DE GROSSESSE CONFIDENTIEL
ANTECEDENTS ET DEBUT DE GROSSESSE
(réservé aux professionnels de santé)

FERRING
PRODUITS PHARMACEUTIQUES

Etude n° : _____ Observatoire : _____ Numéro de Centre : _____ Numéro de Patient : ____	**N° FERRING S.A.S. :** **Type de rapport :** ☐ Initial ☐ Suivi n°_____

INFORMATIONS SUR LA PATIENTE

Deux premières lettres du nom de famille	*Date de naissance* Jour | Mois | Année	*Age*	*Taille* cm	*Poids* kg

INFORMATIONS SUR LE MEDICAMENT PRIS PENDANT LA GROSSESSE

Nom du médicament	*Forme*	*Numéro de lot*	*Date d'expiration*

Posologie quotidienne	*Voie d'administration*

Indication	*Durée du traitement*		
	Date de début (JJMMAAAA)	Date de fin (JJMMAAAA)	**En cours**
			☐

AUTRES TRAITEMENTS CONCOMITANTS

Nom du médicament	Voie d'administration	Schéma posologique	Date de début			En cours	Date de l'arrêt			Indication
			Jour	Mois	Année		Jour	Mois	Année	
						☐				
						☐				
						☐				
						☐				

EVENEMENT(S) INDESIRABLE(S)

La patiente a-t-elle présenté un(des) évènement(s) indésirable(s) nécessitant d'être rapporté(s) ? ☐ Oui ☐ Non

Si oui, préciser :

.....
.....
.....
.....
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Version 3

FORMULAIRE DE GROSSESSE CONFIDENTIEL
ANTECEDENTS ET DEBUT DE GROSSESSE
(réservé aux professionnels de santé)

FERRING
PRODUITS PHARMACEUTIQUES

GROSSESSES

Antécédents gynécologiques/obstétricaux : .....

.....

.....

.....

Parité : .....

Date des dernières règles : .....

Date de diagnostic de la grossesse : .....

Date présumée de début de grossesse : .....

Accouchement prévu le : .....

CONJOINT

Date de naissance Jour | Mois | Année	*Activité professionnelle*	*Exposition à un environnement particulier (produits toxiques, etc…)*

ANTECEDENTS FAMILIAUX DU COUPLE

	Patiente			*Conjoint*		
Malformations	☐ Oui	☐ Non	☐ Inconnu	☐ Oui	☐ Non	☐ Inconnu
Enfants décédés en bas âge	☐ Oui	☐ Non	☐ Inconnu	☐ Oui	☐ Non	☐ Inconnu
Retard psychomoteur	☐ Oui	☐ Non	☐ Inconnu	☐ Oui	☐ Non	☐ Inconnu
Consanguinité	☐ Oui	☐ Non	☐ Inconnu	☐ Oui	☐ Non	☐ Inconnu
Maladie héréditaire* * *préciser*	☐ Oui	☐ Non	☐ Inconnu	☐ Oui	☐ Non	☐ Inconnu

Autres éléments importants de l'anamnèse (maladies chroniques, allergies…)

.....

.....

.....

.....

SOURCE INFORMATION

Nom, adresse et téléphone de la personne qui rapporte la grossesse	*Date et signature*

« Vos données personnelles font l'objet d'un traitement par FERRING SAS destiné à gérer votre notification. Conformément à la loi « Informatique et libertés » du 6 janvier 1978 modifiée, vous disposez d'un droit d'accès et de rectification à vos données, que vous pouvez exercer auprès du Responsable Juridique par e-mail : service.juridique@ferring.com ou par courrier au 7, rue Jean-Baptiste Clément - 94250 GENTILLY. La pharmacovigilance étant une obligation légale de FERRING SAS, vous ne pouvez pas vous opposer au traitement de vos données. Nous vous prions de bien vouloir transmettre oralement à votre patient(e) les informations ci-dessus en lui précisant qu'elle peut exercer son droit d'accès et de rectification auprès de FERRING SAS par votre intermédiaire ».

A renvoyer au Laboratoire Ferring – Service de Pharmacovigilance – sous 24 h par e-mail : [redacted]

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« Formulaire de grossesse confidentiel déroulement et issue de grossesse »

MO-P-0004.03, Annexe 4
Version 4

FORMULAIRE DE GROSSESSE CONFIDENTIEL
DEROULEMENT ET ISSUE DE GROSSESSE
(réservé aux professionnels de santé)

FERRING
PRODUITS PHARMACEUTIQUES

Etude n° : _____ Observatoire : _____ Numéro de Centre : ___ Numéro de Patient : __	N° FERRING S.A.S. : Type de rapport : ☐ Initial ☐ Suivi n°_____

INFORMATIONS SUR LA PATIENTE

Deux premières lettres du nom de famille	*Date de naissance* Jour | Mois | Année	*Age*	*Taille* cm	*Poids* kg

INFORMATIONS SUR LE MEDICAMENT PRIS PENDANT LA GROSSESSE

Nom du médicament	*Forme*	*Numéro de lot*	*Date d'expiration*
Posologie quotidienne	*Voie d'administration*		
Indication	*Durée du traitement*		
	Date de début (JJMMAAAA)	Date de fin (JJMMAAAA)	En cours
			☐

SUIVI DE LA GROSSESSE

	Résultat échographie *(joindre les comptes rendus si nécessaire)*
1ère date *Jour | Mois | Année*	.....
2ème date *Jour | Mois | Année*	.....
3ème date *Jour | Mois | Année*	.....

EVENEMENTS AU COURS DE LA GROSSESSE

Pathologies au cours de la grossesse : ☐ Oui ☐ Non

HTA	Epilepsie	Diabète	Maladie Psychologique	Infection	Autre (préciser)
☐	☐	☐	☐	☐	

HOSPITALISATION AU COURS DE LA GROSSESSE

☐ Oui ☐ Non

Si oui, raison : .....

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Version 4

FORMULAIRE DE GROSSESSE CONFIDENTIEL
DEROULEMENT ET ISSUE DE GROSSESSE
(réservé aux professionnels de santé)

FERRING
PRODUITS PHARMACEUTIQUES

AUTRES TRAITEMENTS PRIS AU COURS DE LA GROSSESSE

Nom du médicament	Voie d'administration	Schéma posologique	Date de début			En cours	Date de l'arrêt			Indication
			Jour	Mois	Année		Jour	Mois	Année	
						☐				
						☐				
						☐				

ISSUE DE LA GROSSESSE

☐ Avortement provoqué Date : .....
☐ Avortement spontané Date : .....
☐ Accouchement normal par voie basse Date : .....
☐ Accouchement par césarienne Date : .....
Déroulement : .....
.....
.....

NOUVEAU-NE

Scores d'Apgar (1 minute, 5 minutes, 10 minutes) : .....

Sexe : ..... Poids : ..... kg Taille : ..... cm

Le nouveau-né est-il porteur de malformations ou d'anomalies ?
☐ Oui ☐ Non Si oui, décrire les anomalies observées: .....
.....

Pensez-vous qu'il existe une relation de causalité au médicament Ferring, pris par la mère ou le père ?
☐ Oui ☐ Non Si oui, préciser : .....
.....

Le nouveau-né a-t-il reçu un traitement correcteur ?
☐ Oui ☐ Non Si oui, préciser le(s)quel(s) : .....
.....

Evolution de l'anomalie : .....
.....

COMMENTAIRES

.....
.....
.....

SOURCE INFORMATION

Nom, adresse et téléphone de la personne qui rapporte la grossesse	*Date et signature*

«Les données recueillies dans le cadre de la Pharmacovigilance sont susceptibles d'être enregistrées. Ces informations sont réservées à l'usage unique du Laboratoire. Conformément à la loi informatique et libertés n°78-17 du 6 janvier 1978 modifiée, vous disposez d'un droit d'accès et de rectification des données à caractère personnel vous concernant. Vous pouvez exercer ce droit en adressant un courrier au Service Juridique du Laboratoire Ferring au 7, rue Jean-Baptiste Clément 94250 Gentilly. »

A renvoyer au Laboratoire Ferring – Service de Pharmacovigilance – sous 24 h par e-mail : [redacted]

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Annex 6 : EQ-5D health questionnaire

Veuillez indiquer, pour chacune des rubriques suivantes, l'affirmation qui décrit le mieux votre état de santé aujourd'hui, en cochant la case appropriée.

Mobilité

Je n'ai aucun problème pour me déplacer à pied ❑
J'ai des problèmes pour me déplacer à pied ❑
Je suis obligé(e) de rester alité(e) ❑

Autonomie de la personne

Je n'ai aucun problème pour prendre soin de moi ❑
J'ai des problèmes pour me laver ou m'habiller tout(e) seul(e) ❑
Je suis incapable de me laver ou de m'habiller tout(e) seul(e) ❑

Activités courantes *(exemples: travail, études, travaux domestiques, activités familiales ou loisirs)*

Je n'ai aucun problème pour accomplir mes activités courantes ❑
J'ai des problèmes pour accomplir mes activités courantes ❑
Je suis incapable d'accomplir mes activités courantes ❑

Douleurs / gêne

Je n'ai ni douleur ni gêne ❑
J'ai des douleurs ou une gêne modérée(s) ❑
J'ai des douleurs ou une gêne extrême(s) ❑

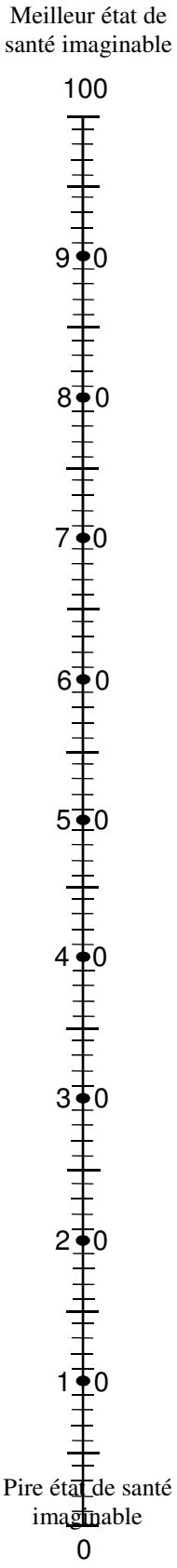
Anxiété / Dépression

Je ne suis ni anxieux(se) ni déprimé(e) ❑
Je suis modérément anxieux(se) ou déprimé(e) ❑
Je suis extrêmement anxieux(se) ou déprimé(e) ❑

Pour vous aider à indiquer dans quelle mesure tel ou tel état de santé est bon ou mauvais, nous avons tracé une échelle graduée (comme celle d'un thermomètre) sur laquelle 100 correspond au meilleur état de santé que vous puissiez imaginer et 0 au pire état de santé que vous puissiez imaginer.

Nous aimerions que vous indiquiez sur cette échelle où vous situez votre état de santé aujourd'hui. Pour cela, veuillez tracer une ligne allant de l'encadré ci-dessous à l'endroit qui, sur l'échelle, correspond à votre état de santé aujourd'hui.

Votre état de santé aujourd'hui



Annex 7 : Register

N° de centre : |__|__|

REGISTRE D'INCLUSION ET DE NON INCLUSION

Veuillez reporter ci-dessous les patients répondant aux critères de sélection de l'étude et présélectionnés pour l'étude DUO, par ordre chronologique de visite de consultation, en indiquant, le cas échéant, le motif de non inclusion dans l'étude.

N°	Date de consultation	Age	Classification TNM	Inclus dans l'étude DUO	Si NON, motif principal de non inclusion
1.	|_|_|/|_|_|/|_|_|_|_| jj mm aaaa	|__|__| ans	|_T|__|_N|__|_M|__|	❑ Oui ❑ Non ➔	❑ Oubli du médecin ❑ Refus du patient ❑ Autre, à préciser :
2.	|_|_|/|_|_|/|_|_|_|_| jj mm aaaa	|__|__| ans	|_T|__|_N|__|_M|__|	❑ Oui ❑ Non ➔	❑ Oubli du médecin ❑ Refus du patient ❑ Autre, à préciser :
3.	|_|_|/|_|_|/|_|_|_|_| jj mm aaaa	|__|__| ans	|_T|__|_N|__|_M|__|	❑ Oui ❑ Non ➔	❑ Oubli du médecin ❑ Refus du patient ❑ Autre, à préciser :
4.	|_|_|/|_|_|/|_|_|_|_| jj mm aaaa	|__|__| ans	|_T|__|_N|__|_M|__|	❑ Oui ❑ Non ➔	❑ Oubli du médecin ❑ Refus du patient ❑ Autre, à préciser :

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N° de centre : |__|__|

N°	Date de consultation	Age	Classification TNM	Inclus dans l'étude DUO	Si NON, motif principal de non inclusion
5.	|_|_|/|_|_|/|_|_|_|_| jj mm aaaa	|__|__| ans	|_T_|__|_N_|__|_M_|__|	❑ Oui ❑ Non ➔	❑ Oubli du médecin ❑ Refus du patient ❑ Autre, à préciser :
6.	|_|_|/|_|_|/|_|_|_|_| jj mm aaaa	|__|__| ans	|_T_|__|_N_|__|_M_|__|	❑ Oui ❑ Non ➔	❑ Oubli du médecin ❑ Refus du patient ❑ Autre, à préciser :
7.	|_|_|/|_|_|/|_|_|_|_| jj mm aaaa	|__|__| ans	|_T_|__|_N_|__|_M_|__|	❑ Oui ❑ Non ➔	❑ Oubli du médecin ❑ Refus du patient ❑ Autre, à préciser :
8.	|_|_|/|_|_|/|_|_|_|_| jj mm aaaa	|__|__| ans	|_T_|__|_N_|__|_M_|__|	❑ Oui ❑ Non ➔	❑ Oubli du médecin ❑ Refus du patient ❑ Autre, à préciser :

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N° de centre : |__|__|

N°	Date de consultation	Age	Classification TNM	Inclus dans l'étude DUO	Si NON, motif principal de non inclusion
9.	|_|_|/|_|_|/|_|_|_|_| jj mm aaaa	|__|__| ans	I_T_I__I_N_I__I_M_I__I	❑ Oui ❑ Non ➔	❑ Oubli du médecin ❑ Refus du patient ❑ Autre, à préciser :
10.	|_|_|/|_|_|/|_|_|_|_| jj mm aaaa	|__|__| ans	I_T_I__I_N_I__I_M_I__I	❑ Oui ❑ Non ➔	❑ Oubli du médecin ❑ Refus du patient ❑ Autre, à préciser :
11.	|_|_|/|_|_|/|_|_|_|_| jj mm aaaa	|__|__| ans	I_T_I__I_N_I__I_M_I__I	❑ Oui ❑ Non ➔	❑ Oubli du médecin ❑ Refus du patient ❑ Autre, à préciser :
12.	|_|_|/|_|_|/|_|_|_|_| jj mm aaaa	|__|__| ans	I_T_I__I_N_I__I_M_I__I	❑ Oui ❑ Non ➔	❑ Oubli du médecin ❑ Refus du patient ❑ Autre, à préciser :

Nom / Prénom Date Signature

Document à transmettre à Axonal-Biostatem à la fin de l'étude

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