Cover page for Protocol

Sponsor name	Ferring Pharmaceuticals A/S
NCT Number	NCT05181800
Sponsor trial ID:	000351
Official title of study	A Multi-center, Single-arm, Non-interventional Study to Describe the Safety of FIRMAGON® (Degarelix Acetate for Injection) in Chinese Patients with prostate cancer and need Androgen Deprivation Therapy
Document Date	11 May 2020

Non-Interventional Study Protocol

Title: A Multi-center, Single-arm, Non-interventional Study to Describe the Safety of FIRMAGON® (Degarelix Acetate for Injection) in Chinese Patients with prostate cancer and need Androgen Deprivation Therapy

Short title: FIRMAGON® Intensive Drug Monitoring Protocol

Study ID: 000351

Sponsor: Ferring Pharmaceuticals (Asia) Co.,Ltd.

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Study phase: IV, Post-Approval Company Sponsored (Observational)

Date of version 1.0 of protocol: 11-May-2020

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Study summary

International Nonproprietary Name: Degarelix Acetate for Injection	**Brand name:** FIRMAGON®
Formulation and specification: (1)80mg; (2)120mg (Calculated by Degarelix)	**Compound:** Degarelix
Date of first approval in China: 2018.9.11	**New drug monitoring period:** 2018.9.11-2023.9.10
Date to domestic market: 2019.04	**International Birth Day:** 2008.12.24
Reason for Monitoring: Per regulatory authority's requirement of drug intensive monitoring for all new approval products	**Implementation provinces:** Nationwide
Start Date: Q1 2021	**End Date:** Dec 2022
Financial support: Ferring Pharmaceuticals (Asia) Co.Ltd.	**Total expenditure:** Undetermined
Study Number: 000351	**Phase:** IV
Sponsor: Ferring Pharmaceuticals (Asia) Co.,Ltd. **Address:** 19th Floor, Century Link Tower One, 1198 Century Avenue, China (Shanghai) Pilot Free Trade Zone PPD **Phone Number:** + 86 021-80303001 PPD	
Submission of Information: FIRMAGON® intensive drug monitoring protocol: Version 1.0, 11-May-2020 Plan Protocol submission to national ADR Monitoring Center: June-2020	
Objective: • To evaluate the safety profile of FIRMAGON® (to fulfill the regulatory authority's requirement of Intensive Drug Monitoring in Chinese patients with prostate cancer need androgen deprivation therapy treated with FIRMAGON®)	
Outcomes: • To evaluate safety and tolerability of degarelix one-month dosing regimen in Chinese patients diagnosed with prostate cancer and need Androgen Deprivation Therapy.	
Summary of study methods:	

- **Study Design**

This study is a multi-center, single-arm, non-interventional, prospective study among Chinese patients with prostate cancer and need androgen deprivation therapy receiving treatment with FIRMAGON®. This program will provide the minimum 6 doses and maximum 12 doses of FIRMAGON® to enrolled patients during one-year follow-up. Patients who meet inclusion criteria and will or are accepting at least 6 self-financed doses treatment in hospital. Patients should return to the hospital for medical assessment every three months. The prescription of 6 (3 dose × 2 times) self-financed doses will be given by doctors after assessment, and the direct-to-patient pharmacy will distribute FIRMAGON® to eligible patients (patients should bring the prescriptions and the last FIRMAGON® boxes to get other doses). All enrolled patients will be followed up to collect safety information for one year from the 1st dose unless withdrawal of Informed Consent Form, discontinuation for 2 months, lost to follow-up, death, or termination due to other reasons, whichever comes first.

- Study sites

Data will be collected by China Primary Healthcare Foundation from patients or Health care providers (HCPs). 138 target hospitals are in the charity support list.

- Patients number

2500 patients who are prescribed FIRMAGON® according to clinical practice by doctors in hospitals will be enrolled in this study.

- Main Inclusion Criterion

Patients must meet all the criteria listed below to be eligible for participation in the project.

  - Diagnosis with prostate cancer and need androgen deprivation therapy
  - Decision made to prescribe of FIRMAGON® prior to enrolment.
  - Willingness and ability to provide written informed consent.
  - The patients are from whom taken post-marketing drug FIRMAGON®.

- Main Exclusion Criterion

Any patient who meets the following criterion will not be qualified for the entry of this study:

  - Not sign Informed Consent.
  - Any patients who is unsuitable to participate in this study because of any other reasons will not be qualified to participate in this study.

- Data collection

The data below will be collected based on the current clinical practice and no additional data, diagnostic or monitoring procedures are applied to the patients.

  - Patient demographic information of age

- Disease characteristics: PSA and Testosterone
- Treatment: detail of FIRMAGON®, medical history and concomitant medications
- Adverse events after FIRMAGON® treatment: AE name, start date, end date, ~~severity,~~ serious or non-serious, causality, actions to FIRMAGON®, treatment due to AE, outcome, etc.

- Data management

In this study, all enrolled patient demographic information will be recorded in charity's database. AE data will be filled in Adverse Event Form (as Appendix 1), processing in safety database and submitting to relevant authorities. Data will be regularly checked to ensure the quality.

- Study schedule

Planned Start of Study:	Q1 2021
Planned the end of the last patient's follow-up:	Aug 2022
Planned completion of the Study Report:	Dec 2022

Conclusion of Intensive Drug Monitoring Study:

Remarks:

List of Abbreviations and Definition of Terms

AE	Adverse Event
ADR	Adverse Drug Reaction
CA	Competent Authority
CRO	Contract Research Organisation
HCP	Health care provider
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDM	Intensive Drug Monitoring
IEC	Independent Ethics Committee
MAH	Marketing Authorization Holder
NMPA	National Medical Products Administration
GPP	Pharmacoepidemiology practice
PSA	Prostate specific antigen
PV	Pharmacovigilance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
UAT	User Acceptance Test

1 Introduction

1.1 Clinical background

Prostate cancer is one of the most common types of cancer in men. Usually prostate cancer grows slowly and is initially confined to the prostate gland, where it may not cause serious harm. However, while some types of prostate cancer grow slowly and may need minimal or even no treatment, other types are aggressive and can spread quickly. Worldwide, prostate cancer is the second most frequently diagnosed cancer among men with estimated 914,000 new cases (13.8% of total) and 258,000 deaths in 2008. The incidence rate varies more that 25-fold worldwide, highest in Western Europe, Australia & New Zealand and US and lowest in South-Central Asia. The majority of cases occur in developed countries[6]. The estimated new cases and deaths the Europe in 2008 are 382,300 and 89,300 representing 22.2% of new cancer cases and 9.3% of cancer deaths in men, respectively[7]. The estimated new cases and deaths in US in 2012 are 241,740 and 28,170, representing 29% of new cancer cases and 9% of cancer deaths respectively[8]. The variation in incidence rates is also pronounced within Europe with the highest rate in Ireland and the lowest in Greece; age-standardize incidence rates of 183.1 and 31.1 per 100,000, respectively, in 2008. Patterns of mortality rates largely reflect those of incidence rates, but with less variation between countries[9]. See detail information from risk management plan - RMP for Degarelix (V16.0, 12 Jul 2019).

In recent years，the incidence of prostate cancer has shown an obvious growth trend in China. In 2008, the incidence of prostate cancer of Chinese men was 11.00/100 000, accounting for 3.33％of the incidence of men’s malignant tumors; the incidence of urban males was about 3.7 times of that in rural areas; the results of age-specific incidence showed that the incidence of Chinese males over the age of 70 ranked the first place in the males genitourinary tumor; the growth incidence rate of urban men with prostate cancer was 8.53/100 000, higher than 2.53/100 000 in rural areas; the proportion of high age group was increased significantly in the age composition of the incidence over time[10].

1.2 Medicinal products

FIRMAGON® (Degarelix) is a synthetic linear decapeptide amide containing seven unnatural amino acids, five of which are D-amino acids. FIRMAGON® is a gonadotrophin releasing

hormone (GnRH) antagonist (receptor blocker), and as such blocks the GnRH receptor to induce a rapid decrease in release of LH and FSH from the pituitary, leading to a fast, profound and sustained suppression of testosterone and Prostate specific antigen (PSA) without an initial testosterone surge. No materials used in the synthesis of Degarelix are of human or animal origin.

1.3 Preliminary safety assessment results

Domestic Clinical Trials

The safety of Degarelix was investigated in a China Phase III active-controlled trial in Chinese patients (N = 283) receiving monthly Degarelix (subcutaneous injection) or Goserelin (subcutaneous injection) for 12 months. Adverse events reported in >=5% patients were showed in Table 1.

Table 1, Adverse Events occurred in >=5% Patients in the Groups by MedDRA System Organ Class and Preferred Term - Safety Analysis Set

	Degarelix 240/80mg (S.C.) N=142	Goserelin 3.6mg (S.C.) N=141
Any Adverse Event	76.1%	58.9%
General Disorder and administration site condition		
Injection site reactions	45.1%	1.4%
Injection Site Swelling	26.8%	0.7%
Injection Site Erythema	26.8%	
Injection Site Pain	24.6%	0.7%
Injection Site Mass	7.0%	
Pyrexia	12.7%	1.4%
Fatigue	5.6%	2.1%
Infections and Infestations		
Urinary tract infection	7.0%	7.8%
Vascular Disorders		
Hypertension	9.9%	10.6%

MedDRA version 18.0

The most common adverse events in patients treated with Degarelix were injection site reactions, including injection swelling (26.8%), injection site erythema (26.8%), injection site pain (24.6%), and injection site mass (7.0%).

Most injection site reactions were mild or moderate in severity (2 patients with severe injection site reactions: 1 with severe injection erythema and 1 with severe injection site mass), and there is no hypersensitivity reaction of immediate onset. Adverse events mainly occurred in the initial stage of treatment, and their incidences were decreased with time. No patients discontinued from the trial due to injection site reactions.

Of abnormalities in hepatic function test, alanine aminotransferase (ALT) (with or without total bilirubin), aspartate aminotransferase (AST), and total bilirubin were comparable between the treatment groups. No patient developed increased ALT considered as serious adverse event, and no patient discontinued from the trial due to increased ALT.

ECG results showed that, there was no significant differences of mean change of QTcF between the treatment groups from baseline to Day 3 and to the end-of-trial visit. QTcF >=500 msec occurred in 13 patients, including 7 (5%) patients in the Degarelix Group and 6 (4%) patients in the Goserelin Group.

Overall, the safety results from the trial were consistent with those of foreign pivotal studies, and were also consistent with the expected results in elderly patients of prostate cancer receiving androgen therapy; mo major safety problems were found.

Available data from clinical trials indicates that FIRMAGON® is generally well tolerated, with adverse events (AEs) generally being manageable and reversible with supportive care. The adverse event profile is similar to that of the GnRH agonists with the most frequently reported adverse drug reactions (ADRs) being related to the pharmacological activity of the product (testosterone inhibition). See detail information from China label of Degarelix .

Regulatory requirements

The China National Medical Products Administration (NMPA) on 11 Sep, 2018 formally approved the Marketing Authorization Application of imported FIRMAGON® in China. Due

to the requirements on "Regulations for the Reporting and Monitoring of Adverse Drug Reactions" and the "Intensive Drug Monitoring Guidelines for Manufacturers", Marketing Authorization Holder (MAH) should report all adverse reactions and conduct intensive monitoring for new imported drugs within 5 years from the date of first approval.

Intensive Drug Monitoring (IDM) refers to drug safety monitoring activities carried out to further understand clinical use of drug, the occurrence of ADRs and its occurrence of characteristics or seriousness or incidence in real world practice. Based on the consideration, Ferring Pharmaceuticals (Asia) Co.,Ltd. (hereinafter referred to as "Ferring") plans to carry out IDM study and collect all patients' AEs whether or not related to the product use, with particular attention to the occurrence of important adverse reactions.

2 Study Objective and Outcome measure

2.1 Objective

This safety research study focuses on the safety information used in the real world, based on known risks. The occurrence of adverse events of FIRMAGON® will be evaluated.

2.2 Outcome measure

- To evaluate safety and tolerability of degarelix one-month dosing regimen in Chinese patients diagnosed with prostate cancer and in need of Androgen Deprivation Therapy.

For the definition of SAEs/AEs, see section 6.

3 Study Administrative Structure

In accordance with the "Regulations for the Reporting and Monitoring of Adverse Drug Reactions" and the "Intensive Drug Monitoring Guidelines for Manufacturers", the intensive monitoring for FIRMAGON® is initiated by Ferring, aimed to evaluate patient safety of using FIRMAGON® treatment in real-world practice. To this end, the Ferring has arranged members of related internal departments and delegated a Contract Research Organization (CRO) for monitoring drug safety. Before the study is implemented, it will be filed with the National Adverse Drug Reaction Monitoring Center.

3.1 Study Sites

This study is to select qualified hospitals which have signed contract with China Primary Healthcare Foundation as study sites. 138 target hospitals are in the charity support list. The charity will provide FIRMAGON® to patients who participate in this study. In order to ensure the representativeness of the sample, participating sites will cover all major regions across China, and China Primary Healthcare Foundation is recommended to enroll patients on a consecutive basis. The CRO will keep a record of the individuals responsible for each participating Study Site.

4 Ethics

This study is an observational study where the existence of the study has no impact on the patient except for collection of informed consent to use patients' data. Informed Consent Form (ICF) will be reviewed and recorded by Central EC.

4.1 Ethical conduct of the Study

This study will be conducted in accordance with the protocol, the current version of the Declaration of Helsinki, Good Pharmacoepidemiology Practices (GPP), ISPE GPP guideline and any local regulations.

Ferring will ensure that the protocol, the patient Information Sheet/ICF and any amendments are submitted to the Independent central Ethics Committees (IECs) according to local requirements.

According to applicable regulations, we will:

- notify or obtain approval from the relevant IEC of the protocol, the patient Information Sheet/ICF and any amendments
- submit required documents to the IEC, such as:
    - ✓ protocol deviation, safety information or summary of the study progress according to the requirement (if applicable)
    - ✓ notification of the end-of-study
    - ✓ a summary of the study results

Ferring will keep an updated list of all submissions and approval dates of all documents submitted to the IEC and will provide the Site Responsible with a copy of this list. Copies of the documents will be distributed upon request.

4.2 Authorities

Ferring will send required documents to the regulatory authority and keep an updated list of submission and approval dates and a copy of all documents submitted.

4.3 Patient Information and Written Informed Consent

This study is an observational study, even though patients will return to hospital and accept monthly FIRMAGON® treatment, the staff of the charity must give the patient oral and written information about the study in a form that the patient can understand and obtain the patient's written consent before collection of identifiable patient information (hereinafter referred to as personal data). Before consenting, the patient must be left with ample time to consider and to pose questions. Since the study is observational, the consent only concerns the data collection The decision to treat the patient is independent of the decision to enrol the patient in the study.

The patient must agree that Ferring personnel, their representatives or IEC or regulatory authority personnel may require direct access to the patient's data / personal records which were collected, processed and stored in an anonymous form.

The patient must agree that his / her data will be processed and stored in an anonymous form for evaluation of this study and any later overviews. Data may also be transferred in anonymous form to third parties, e.g. other companies or authorities, that may be located in other countries with potentially different regulations for data.

The patient will receive a copy of ICF after consenting.

The patient has the right to withdraw their consent at any time without prejudice. In the Informed Consent Form it is stated that if consent is withdrawn, any data collected before withdrawal of consent will be kept. The original Informed Consent Forms signed and dated by the patient and investigators must be kept in the Charity.

For details, see the Informed Consent Form.

5 Study Design and Plan

This study is a multi-center, single-arm, non-interventional study among Chinese patients with prostate cancer needed androgen deprivation therapy receiving treatment with FIRMAGON®. 2500 patients who are prescribed FIRMAGON® according to clinical practice by doctors in hospitals will be enrolled in this study. This program will provide the minimum 6 doses and maximum 12 doses of FIRMAGON® to enrolled patients during one-year follow-up. Patients apply for enrollment in hospital, they will return to hospital every three months for medical assessment and other three doses of FIRMAGON® prescription during the study. 138 target hospitals are in the charity support list. The direct-to-patient pharmacy will distribute FIRMAGON to patients who are defined eligible by the doctor. The patient should bring the prescriptions and the last FIRMAGON® boxes to get other FIRMAGON®.

All enrollment patients will be followed up to collect safety information for one year from China Primary Healthcare Foundation from the 1st dose unless withdrawal of Informed Consent Form, dosing interrupted for 2 months or more than 2 months since last dose, lost to follow-up, death, or termination due to other reasons (defined in section 5.4), whichever comes first. Any AEs will be filled in Adverse Event Form (as Appendices), processing and submitting to relevant authorities.

5.1 Study Schedule

Planned Start of Study: Q1 2021

Planned the end of the last patient's follow-up Aug 2022

Planned completion of the Study Report: Dec 2022

The Ferring will ensure that End-of-Study notification is submitted to the concerned authorities and IEC for each site as locally required.

5.2 Discussion of Study Design

This IDM study is a non-interventional study to collect all AEs during the post-marketing drug use.

AE data collection is the main purpose of the IDM programme. For all patients, the key outcome measure is to evaluate the safety profile of FIRMAGON® in Chinese population in real world clinical practice.

In reality, the willingness of hospitals to accept post-marketing trials is not high, and it is difficult to enroll patients as well. Therefore, to fulfill regulatory requirements within timeline, considering to combine the IDM with China Primary Healthcare Foundation. In this study, due to enrollment of low-income patients with prostate cancer, the possibility of population selection bias must be considered.

The sample size sets as 3000 patients or cover 80% of the patient exposure, meet either of these two regulation requirements. Due to the low sales volume forecast, the sample size could be decreased to 2500 patients per discussion with authority officer. The supportive documents will be provided if there any other post-marketing surveillance study reports available. In any a hospital participates in this program, most of its patients might have access to obtain FIRMAGON® donations.

Although patients included in this study might not receive any direct benefit from the study, the study will promote better understanding of the safety FIRMAGON® for prostate cancer needed androgen deprivation therapy patients in a large, more generalizable population.

5.3 Selection of Study Population

5.3.1 Inclusion Criteria

Patient eligibility is determined according to the following criteria prior to entry into the study:

1) Diagnosis as prostate cancer and need androgen deprivation therapy
2) Decision made to prescribe of FIRMAGON® prior to enrolment.
3) Willingness and ability to provide written informed consent.
4) The patients are from whom taken post-marketing drug FIRMAGON®.

5.3.2 Exclusion Criteria

Any patient who meets the following criterion will not be qualified for entry in this study:

1) Not signed Informed Consent.

2) Any patients who is unsuitable to participate in this study because of any other reasons will not be qualified to participate in this study.

5.4 Patient Discontinuation

The following events will result in patient discontinuation and should be recorded in the study database:

1) The doctors confirm that the patient does not meet the instructions of FIRMAGON® or is unsuitable for continued use;
2) The patient presents an intolerable adverse reaction;
3) Death;
4) The patient, his legal guardian or immediate family request the discontinuation of FIRMAGON® treatment;
5) The patient refuses to accept medical evaluation according to the procedure or protocol;
6) The patient automatically removes from the group after 2 months discontinuation of medication;
7) The patient sales, exchanges the donation drugs for profit purposes;
8) The application information provided by patients is confirmed as false information, including application form with patient's information, medical information (medical history, diagnoses, treatment, etc.) and follow up information, etc; ;
9) The application is not within the time limit, or all the donation drugs have been distributed within cutoff day;
10) Suspension due to the policy adjustments or changes from regulatory authority.

5.5 Premature Trial Termination

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

In addition, the sponsor reserves the right to terminate the participation of individual trial sites.

Conditions that may warrant termination include, but are not limited to, insufficient adherence to protocol requirements and failure to enter patients at an acceptable rate.

5.6 Study Plan

Data collection overview:

Frequency	Inclusion	Every 3 months during total 12 months
Visit Window	The Baseline Visit	The 2nd Visit to the 4th Visit
Obtaining informed consent	X	
Inclusion/Exclusion criteria	X	
Demographic information[1]	X	
Medical history[2]	X	
Disease characteristics[3]	X	
FIRMAGON® treatment[4]	X	X
AE collecions[5]	X	X
Disease condition[6]	X	X

Definitions:

1. Including age and domicile place.
2. Including general medical history, surgical history, metastasis situation.
3. Prostate cancer: stage, the date of histology diagnosis, Gleason Score, presenting symptoms.
4. FIRMAGON® treatment information: initial dose and time, duration, dose adjustment (actions, times and reasons). Details need be collected for permanent withdrawal patients.
5. AE name (Verbatim term, SOC, PT), reporter info, event onset date, event stop date, action taken, outcome, seriousness, causality, medical history, concomitant medications.
6. Including the level of Serum PSA and Testosterone, and questions about disease progress or remission?

6 Safety Reporting

6.1 Definitions

6.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any untoward and unintended sign (including an abnormal laboratory finding), symptom, a new disease or worsening in severity or frequency of a concomitant disease, temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product. In this study, all AEs (including Serious Adverse Events) after first dose of FIRMAGON® should be collected.

Abnormal laboratory values or outcome of an examination considered as clinically significant by HCP should be reported as an AE.

6.1.2 Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (NOTE: The term “life-threatening” in the definition of “serious” refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or results in prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a medically important event or reaction

  Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the

definition above. Examples of such events are intensive treatment in an emergency room or at home for hypersensitivity, anaphylactic reaction, angioedema that do not result in hospitalization, or development of drug dependency or drug abuse.

6.1.3 Adverse Drug Reactions

An adverse drug reaction (ADR) is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

6.2 Relationship of an AE to studied drug(s)

When dealing with adverse events, data collector should make full use of known medical knowledge and clinical experience to conduct a comprehensive analysis and evaluate the association of adverse events with FIRMAGON®. The possibility of whether the studied drug caused the adverse event must be classified as one of the following:

- **Reasonable possibility:**

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

Examples:

Adverse events that are uncommon but are known to be strongly associated with exposure to the studied drug.

Adverse events that are not commonly associated with exposure to the studied drug, 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 studied drug and the adverse event.

Examples:

Known consequences of the underlying disease or condition under investigation.

Adverse events common in the study population, which are also anticipated to occur with some frequency during the course of the study, regardless of exposure to the studied drug.

6.3 Collection and Recording of Adverse Events

The safety data will be actively collected in accordance with the follow-up time in the study plan. Patients and HCPs could report AE spontaneously after follow-up time. Collection and recording of SAEs and AEs will commence once the study participant has started first dose of FIRMAGON®.

6.4 Reporting of Adverse Drug Reactions to Regulatory Agencies

China Primary Healthcare Foundation will send the collected safety information Form (AEs and SAEs) to CRO within 1 calendar day. CRO will translate it into English version and transfer to Ferring Global Pharmacovigilance (GPV) for case processing. Ferring is responsible for submission of ADRs to regulatory authorities in accordance with local reporting requirements. As requirement from Chinese authority, the reporting timelines are following:

Serious (Death/cluster): Immediately (death/cluster is detail explained in Data Collection Flow section)

Serious: 15 days

Non-Serious: 30 days

Date 0 is when China Primary Healthcare Foundation becomes aware of an event arising after FIRMAGON® treatment. Events will be collected and sent to GVP within 3 calendar days for serious and 5 calendar days for non-serious. GPV will process the cases and generate CIOMS form on the condition of the event with the causality of FIRMAGON®. For serious, CIOMS form should be sent to local PV within 10 calendar days for submission and 25 calendar days for non-serious.

Data Collection Flow

For Death case:

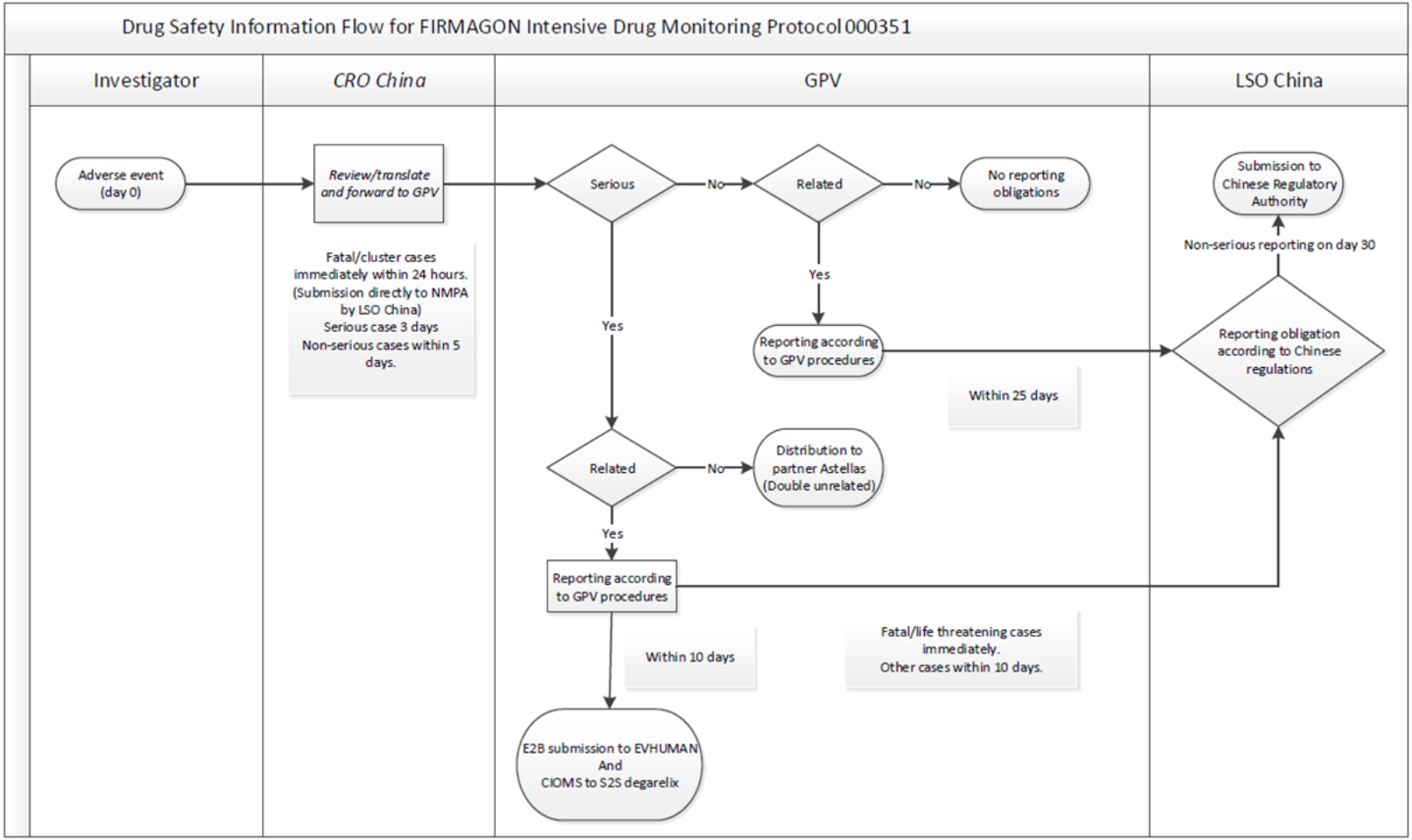
Ferring local PV will inform China regulatory authorities immediately regarding deaths considered related to Firmagon treatment. The investigation will be completed within 15 working days.

For cluster (group) case:

Ferring local PV will inform China regulatory authorities immediately regarding any cluster related cases. Meanwhile, complete the Basic Information Form of Cluster Drug Adverse Events. Then, complete the Drug Adverse Reaction/Event Form for each patient timely.

Cluster of adverse drug events definition: an event which occurs in a relatively concentrated time period and area, damaging or threatening the health or life of a certain number of people during or after use of the same drug, and which requires emergency treatment. The same drug refers to a drug which is produce by the same manufacturer with the same drug name and is in the same formulation and strength. The event number should be above 2.

For other serious and non-serious case:


Drug Safety Information Flow for FIRMAGON Intensive Drug Monitoring Protocol 000351
Investigator
CRO China
GPV
LSO China
Adverse event (day 0)
Review/translate and forward to GPV
Fatal/cluster cases immediately within 24 hours. (Submission directly to NMPA by LSO China)
Serious case 3 days
Non-serious cases within 5 days.
Serious
No
Related
No
No reporting obligations
Yes
Reporting according to GPV procedures
Within 25 days
Yes
Related
No
Distribution to partner Astellas (Double unrelated)
Yes
Reporting according to GPV procedures
Within 10 days
Fatal/life threatening cases immediately.
Other cases within 10 days.
E2B submission to EVHUMAN And CIOMS to S2S degarelix
Submission to Chinese Regulatory Authority
Non-serious reporting on day 30
Reporting obligation according to Chinese regulations

The flow is as following:

(1) Database establishment: the charity's database will be used as study database for this study.

(2) Data entry: the delegated staff will collect data and login the system for data entry. CRO check each information against source data. When any inconsistency is found, a query will be sent to the charity. The data collector should correct data to ensure that the data in the database is consistent with the source record.

(3) Procedure for safety report: each AE report will be filled in AE Form and sent to CRO for creating safety report and translation. The CRO will send English version report by email to Ferring GPV Case Processing via Safety.Mailbox@ferring.com. That reports requiring timely submission to authorities according to Chinese reporting requirements will be delivered to CRO for further process.

(4) CRO will check the data regularly to ensure the quality of data.

7 Data Quality Control and Assurance

7.1 Quality Control

7.1.1 Study design

Before the implementation of the IDM study, the medical affairs system will organize expert and carry out demonstration. During the monitoring, the protocol may be amended according to the prescribed procedure.

7.1.2 Personnel qualifications

Project personnel will be suitably qualified for the tasks assigned to them, the relevant professional background of epidemiology, statistics, pharmacy, clinical medicine are requested. According to IDM study, design a training plan and train the correlate person for quality control.

7.1.3 Reports and Archiving of Study Documentation

All raw materials need to be preserved. The data in study database comes from the original file and is consistent with original. CRO will conduct reconciliation periodically during the study. All observations and lab results should be completed timely, exactly, correctly, normatively. The data must not be changed at will. All documents will be kept for 10 years by specialist.

7.1.4 Statistical Analysis

Professional bio-statisticians are involved in each stage of the IDM study. The process and the expression of the results must be standardized. The missing, unused, or redundant data must be explained. A statistical report will be conducted and be in line with IDM report.

7.2 Audit from Quality Assurance Unit

The Quality Assurance (QA) unit may audit the study to ensure that study procedures comply with the protocol and standard operating procedures, and that collected data is correct and complete.

7.3 Data Management

The patients' data will be input into the charity's database by the delegated staff. The patients will be identified only by Study ID and patient number in the export database for analysis.

If the written informed consent of a patient is known not to be available in spite of it being required, data for this patient is not entered into or is deleted from the export database.

If a patient is included in the study in spite of being treated off-label (not according to the summary of product pharmacological study), data is kept in the database and analysed separately and as part of the overall analyses as described in the Statistical Analysis Plan.

The safety data (AEs report) filed in AE form will be input into global safety database. The current Standard Coding Instructions for coding of medical history, concomitant illness (MedDRA), concomitant medication (WHO-Drug) and adverse events/reactions (MedDRA) must be followed.

8 Statistical Methods and Determination of Sample Size

8.1 General Aspects

All analyses will be performed using SAS version 9.3 or above by the Biostatistician. Numerical data are presented as number of patients, mean, standard deviation, median, min and max. Categorical data are presented as frequency and percentage of patients. Missing data will be analyzed as is, no imputation method will be utilized. The statistical analysis plan will be finalized at least 1 week before the database lock.

8.2 Analysis set

The full analysis set (FAS) will include inpatient or outpatient prostate cancer patients signed informed consent and who need androgen deprivation therapy and have received FIRMAGON® treatment. All analyses will be performed on the FAS population.

8.3 Statistical Methods

Descriptive statistics will be performed of all collected data except data collected only for the purpose of data cleaning. No formal hypothesis will be tested in this study. If necessary, Fisher's exact test, $\chi 2$ test will be used to examine differences in AEs occurrence between subgroups (It will be defined based on the enrollment patients).

8.4 Interim Analyses

No interim analyses are planned for this study.

8.5 Determination of Sample Size

In accordance with the technical requirements stipulated in "Intensive Drug Monitoring Guidelines for Manufacturers" (Annex 2) within the opinion letter "Announcement regarding promoting manufacturers in carrying out intensive drug monitoring work (Draft for comment)" (NMPA Department of Drug Safety Supervisi``on Letter [2013] No. 12) issued by NMPA Department of Drug Safety Supervision on March 25, 2013, no less than 3,000 qualified cases or cover 80% of the patient exposure are planned to be included. Due to the low sales volume forecast, the sample size could be decreased to 2500 patients per discussion with authority

officer. While Ferring will try the best to increase the information integrity and decrease the shedding cases.

9 Reports and Archiving of Study Documentation

A Non-Interventional Study Report based on the results obtained will be prepared and submitted to Global Research for distribution. The Final Study Report should be available within one year from collection of the last data point, and the participating sites should be informed about the results when the report is finalized.

After final database lock the Site Responsible must as a minimum store the list of participating patients and the signed Informed Consent Forms on site for 10 years. The Site Responsible should store additional study documentation for a longer period of time as required by any local regulations and/or hospital requirement.

10 References

1. World Medical Association Declaration of Helsinki. Ethical principles for Medical Research Involving Human Subjects, Helsinki 1964, amended in Tokyo 1975, Venice 1983, Hong Kong 1989, South Africa 1996, Edinburgh 2000, and Seoul 2008.
2. Epstein, M on behalf of ISPE. Guidelines for Good Pharmacoepidemiology Practices (GPP). Pharmacoepidemiology and Drug Safety 2005;14:589-95.
3. National Medical Products Administration. Guidelines for collection and reporting of individual adverse drug reactions. 2018.
4. National Medical Products Administration. Guidelines of Intensive drug monitoring for pharmaceutical manufacturers, 2013..
5. National Cancer Institute. Surveillance, epidemiology, and end results program, Stat Fact Sheets: Myeloma. Accessed 16 MAR 2018. Available at: http://seer.cancer.gov/statfacts/html/mulmy.html
6. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127(12):2893-917.
7. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. Eur J Cancer 2010;46(4):765-81.
8. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012;62(1):10-29.
9. Center MM, Jemal A, et al. International variation in prostate cancer incidence and mortality rates. Eur Urol. 2012 Jun;61(6):1079-92.
10. 韩苏军, 张思维, 陈万青, et al. 中国前列腺癌发病现状和流行趋势分析Analysis of the status and trends of prostate cancer incidence in China[J]. 临床肿瘤学杂志, 018(4):330-334.

11 Appendices

Appendix 1

ADVERSE EVENT REPORT FORM

(Version 6.0. 10-Apr-2019)

GENERAL INFORMATION TO BE COMPLETED BY FERRING LSO/REPORTER/AGENT			
First receipt date: *(Day 0)* Click here to enter a date	**LSO receipt date:** Click here to enter a date	**Country:**	**Local case ID**:
Report type: Add **Post Authorisation studies:*** Add **Study name/Study ID**:	**Serious case:** ☐ Yes ☐ No	**If serious, please specify criteria:** ☐ Patient died ☐ Life threatening ☐ Significant disability ☐ Hospitalisation/prolongation ☐ Congenital anomaly/birth defect ☐ Important medical event	**Other case numbers** ***(Please specify e.g.: Complaint, Regulatory, Partner, etc.)*:** ☐ **Initial** ☐ **Follow-up version:** **Regulatory case:** Yes ☐ No ☐ ***If yes, please state Authority:***
** IIT = Investigator Initiated Trial, MRP = Market Research Program, NIS = Non-Interventional Study, PASS = Post-Authorization Safety Study, PSP = Patient Support Program*			

REPORTER DETAILS		
Health care professional: Yes ☐ No ☐ **If no, please state; has Ferring permission to contact the HCP?** Yes ☐ No ☐	**Reporter type:** Add	**Country:**

PATIENT INFORMATION

Initials:	**Subject number** *(if applicable):*	**Date of birth** (*dd-Mmm-yyyy*)**:**	**Age** *(units)*:	**Gender:** Female ☐ Male ☐	**Weight:** Add **Height:** Add

If pregnant, specify gestational age at onset date of event(s): Add **weeks &** Add **days**

Last menstrual period (LMP) (*dd-Mmm-yyyy*)**:**

RELEVANT MEDICAL HISTORY/PAST DRUG THERAPY/PROCEDURE

	Description of condition	**Start date** (*dd-Mmm-yyyy*)	**Stop date** (*dd-Mmm-yyyy*)	**Result / Comments**	**Ongoing**	
					Yes	**No**
Add					☐	☐
Add					☐	☐
Add					☐	☐
Add					☐	☐
Add					☐	☐
Add					☐	☐
Add					☐	☐
Add					☐	☐
Add					☐	☐

LABORATORY TESTS incl. VITAL SIGNS						
Test name	**Result**	**Units**	**Reference range**		**Test date** (*dd-Mmm-yyyy*)	**Comments**
			Low	**High**		

SUSPECT DRUG(s)										
Trade name and/or generic name. Strength, units & formulation	**Indication**	**Dose & units**	**Frequency**	**Route**	**Batch no. & exp. date**	**Start date** (*dd-Mmm-yyyy*)	**Stop date** (*dd-Mmm-yyyy*)	**Action taken**	***De-****	***Re-****
									Challenge **Did the event abate after stopping the drug? **Did the event reappear after reintroduction?*	
					Add			Add	Add	Add
					Add			Add	Add	Add
					Add			Add	Add	Add
					Add			Add	Add	Add
					Add			Add	Add	Add

CONCOMITANT MEDICATION *(exclude those to treat ADRs)*								
Trade name and/or generic name	**Indication**	**Strength, units & formulation**	**Dose, units & frequency**	**Route**	**Start date** (*dd-Mmm-yyyy*)	**Stop date** (*dd-Mmm-yyyy*)	**Ongoing**	
							Yes	**No**
							☐	☐
							☐	☐
							☐	☐
							☐	☐
							☐	☐
							☐	☐

							☐	☐
							☐	☐
							☐	☐
							☐	☐

Interactions *(if yes, please inform names of the products in question)*

ADVERSE EVENT(s) *(preferably a diagnosis, if not available please provide all the symptoms). If more than one, please enter each event on a separate line*

Adverse Event	Start date (*dd-Mmm-yyyy*)	Stop date (*dd-Mmm-yyyy*)	Intensity	Outcome	Seriousness		Relatedness
					Yes	No	
			Add	Add	☐	☐	Add
			Add	Add	☐	☐	Add
			Add	Add	☐	☐	Add
			Add	Add	☐	☐	Add
			Add	Add	☐	☐	Add
			Add	Add	☐	☐	Add
			Add	Add	☐	☐	Add
			Add	Add	☐	☐	Add
			Add	Add	☐	☐	Add
			Add	Add	☐	☐	Add
			Add	Add	☐	☐	Add

NARRATIVE (*describe chronologically signs, symptoms, relevant medical history, time course and treatment of ADR; include laboratory results of confirmatory procedures without using abbreviations. If patient died, please provide autopsy results).*

Narrative: ***Regulatory narrative?*** *Yes* ☐ *No* ☐

Local Safety Officer comments:	
Completed by:	**Date:** Click here to enter a date
Quality control performed by: *(for Ferring LSO use only)*	**Date:** Click here to enter a date
Translated into English by:	**Date:** Click here to enter a date