# PROTOCOL TITLE: A PHASE III, MULTICENTRE, RANDOMISED, OPEN-LABEL, PARALLEL, ACTIVE-CONTROLLED STUDY TO COMPARE THE OESTRADIOL SUPPRESSION, CLINICAL EFFICACY AND SAFETY OF TWO FORMULATIONS OF TRIPTORELIN (TRIPTORELIN PAMOATE PR 3-MONTH AND TRIPTORELIN ACETATE PR 1-MONTH) IN CHINESE SUBJECTS WITH ENDOMETRIOSIS

STUDY PROTOCOL
STUDY NUMBER: D-CN-52014-220

TRIPTORELIN PAMOATE 15 MG PR

Version 3.0 (Amendment 2.0): 29 September 2017

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## INVESTIGATOR'S AGREEMENT

**Investigator Agreement and Signature:**

I have read and agree to Protocol entitled "A phase III, multicentre, randomised, open-label, parallel, active-controlled study to compare the oestradiol suppression, clinical efficacy and safety of two formulations of triptorelin (triptorelin pamoate PR 3-month[1] and triptorelin acetate PR 1-month[2]) in Chinese subjects with endometriosis". I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME:
TITLE: PRINCIPAL INVESTIGATOR SIGNATURE:

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[ ]
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**Sponsor's Representative Signature:**

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[1] Marketed in China as Triptorelin pamoate for injection 15 mg (for prostate cancer only).
[2] Marketed in China as Diphereline 3.75 mg.

## COORDINATING INVESTIGATOR'S AGREEMENT

**Coordinating Investigator Agreement and Signature:**

I have read and agree to Protocol entitled "A phase III, multicentre, randomised, open-label, parallel, active-controlled study to compare the oestradiol suppression, clinical efficacy and safety of two formulations of triptorelin (triptorelin pamoate PR 3-month and triptorelin acetate PR 1-month) in Chinese subjects with endometriosis". I am aware of my responsibilities as a coordinating investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

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## SUMMARY OF CHANGES

The initial version of the protocol was released on 12 January 2017. The current version of the protocol (Version 3.0) was released on 29 September 2017 and includes Amendment 1.0 (02 May 2017) and Amendment 2.0. The respective protocol amendment forms were prepared and are provided in Appendix 2 and Appendix 3, respectively (Table 1).

**Table 1 List of Protocol Amendments**

| Amendment | Release date | Amendment form |
|---|---|---|
| 1.0 | 02 May 2017 | Appendix 2 |
| 2.0 | 29 September 2017 | Appendix 3 |

## SYNOPSIS

**Name of sponsor/company:** Ipsen Pharma

**Name of finished product:** Triptorelin pamoate prolonged release (PR) 3-month

**Name of active ingredient(s):** Triptorelin pamoate

**Title of study:** A phase III, multicentre, randomised, open-label, parallel, active-controlled study to compare the oestradiol suppression, clinical efficacy and safety of two formulations of triptorelin (triptorelin pamoate PR 3-month and triptorelin acetate PR 1-month) in Chinese subjects with endometriosis

**Study number:** D-CN-52014-220

**Number of planned centres:** Approximately 25 centres in China

| **Planned study period:** | **Phase of development:** |
|---|---|
| May 2017 to November 2019 | Phase III |

**Objectives**:

It is hypothesised that triptorelin pamoate PR 3-month will offer non-inferior efficacy to triptorelin acetate PR 1-month in the treatment of Chinese subjects with endometriosis (as previously demonstrated in a European population in Study E-28-52014-705).

Primary objective:

- To assess the efficacy of triptorelin pamoate PR 3-month formulation in Chinese female subjects with endometriosis by demonstrating the noninferiority of triptorelin pamoate PR 3-month formulation injected once as compared to triptorelin acetate PR 1-month formulation injected 3 times consecutively, assessed by the percentage of subjects castrated (oestradiol ($E_2$) ≤184 pmol/L or 50 pg/mL) at Week 12.

Secondary objectives:

- To assess other efficacy parameters including the percentage of subjects castrated at other time points, $E_2$, luteinising hormone (LH) and follicle stimulating hormone (FSH) concentrations, and the impact on endometriosis-associated pelvic pain.
- To assess the safety profile of triptorelin pamoate PR 3-month.
- To assess the pharmacokinetics (PK) of triptorelin pamoate PR 3-month and compare to triptorelin acetate PR 1-month.

Exploratory objectives:

- To assess efficacy parameters (percentage of subjects castrated, $E_2$, LH and FSH concentrations and impact on endometriosis-associated pelvic pain) after Week 12.
- To explore the PK/pharmacodynamics (PD) of triptorelin pamoate PR 3-month in a subset of subjects (PD markers being $E_2$, FSH and LH).

**Methodology:**

This prospective, multicentre, randomised, open-label, parallel-group, active-controlled study will compare triptorelin pamoate PR 3-month with triptorelin acetate PR 1-month in the treatment of endometriosis in Chinese subjects.

Subjects with endometriosis will be recruited and screened for eligibility up to 5 weeks prior to the first dose of investigational medicinal product (IMP), which must occur during the follicular phase of the menstrual cycle. Eligible subjects will be stratified by endometriotic surgical history and endometriosis-associated pelvic pain (assessed by a visual analogue scale (VAS)) and randomised in a 1:1 ratio to receive either triptorelin pamoate PR 3-month once per 12 weeks or triptorelin acetate PR 1-month once per 4 weeks for a 24-week treatment phase. All subjects will visit the study site every 4 weeks until Week 24, with the exception of the subgroup participating in the full PK and exploratory PD evaluations (up to 32 subjects, including up to 16 from each treatment group; to be enrolled at

selected sites), who will have additional study visits during the treatment phase. If needed in the opinion of the investigator, "add back" treatment (recommended as, but not limited to, tibolone at a dose of 2.5 mg once daily) may be applied from Week 12. After 24 weeks' study treatment, subjects will be followed up by telephone every 4 weeks until menses recovery or Week 40 (whichever is earlier), except for subjects receiving triptorelin pamoate PR 3-month and participating in the full PK/PD subgroup, who will visit the study site. The first visit after the menses recovery or Week 40 will be considered as the end of study visit. All subjects will attend the study site for the end of study visit.

The duration of the study is a minimum of 24 to 40 weeks, plus up to 5 weeks for the screening period.

**Number of subjects planned:**

300 randomised subjects (150 receiving triptorelin pamoate PR 3-month and 150 receiving triptorelin acetate PR 1-month).

**Diagnosis and criteria for inclusion:**

All subjects must fulfil all of the following criteria to be included in the study:

(1) Female subjects aged from 18 to 45 years inclusive at the date of informed consent.

(2) Provided written informed consent.

(3) A history of active and regular menstrual cycles of 21 to 35 days (inclusive) in the 6 months prior to the screening visit.

(4) A diagnosis of endometriosis, confirmed by laparoscopy or laparotomy within 10 years prior to the screening visit.

(5) Requires treatment with a gonadotrophin releasing hormone (GnRH) agonist for a period of 6 months in the judgement of the investigator.

(6) A negative pregnancy test prior to the start of treatment.

(7) Not at risk of pregnancy, i.e. subjects of childbearing potential must be actively using barrier contraception throughout the study treatment until menses resume.

Subjects will be excluded from the study if any of the following apply:

(1) Subject is menopausal.

(2) Subject is pregnant or lactating.

(3) A current history of undiagnosed abnormal genital bleeding.

(4) Received treatment with a GnRH agonist within 6 months prior to the screening visit.

(5) A history of hypersensitivity to GnRH agonists and/or any of the excipients.

(6) Received any other hormonal treatment within 3 months prior to the screening visit (oestrogens, progestogens, danazol, gestrinone and cyproterone acetate etc).

(7) Has been treated for endometriosis with traditional Chinese medicine within 1 month prior to screening.

(8) It is anticipated that the subject will require surgery during the study period.

(9) Chronic pelvic pain that is not caused by endometriosis, that would interfere with the assessment of endometriosis-associated pelvic pain.

(10) A significant endocrine disorder (except controlled diabetes mellitus).

(11) Known history of human immunodeficiency virus (HIV) infection.

(12) Known history of chronic active hepatitis, including viral hepatitis carriers (hepatitis B or hepatitis C).

(13) Clinically significant hepatic (any liver enzyme > 2× the upper limit of normal (ULN)) or renal (creatinine > ULN) abnormalities or any other dysfunction according to the investigator's judgement.

(14) Any psychiatric illness, severe or unstable known illness that in the investigator's opinion could affect the safety, conduct or outcome of the study.

(15) Use of concomitant therapy, which in the investigator's opinion may interfere with the evaluation of study treatment efficacy and safety.

(16) Treatment with any other experimental drug or device within 90 days prior to the screening visit and/or expectation of treatment with any other experimental drug or device during the conduct of the study.

(17) Any malignancy except curatively-treated basal cell skin cancer.

(18) Unable or unwilling to comply with the protocol.

(19) A history of alcohol and/or drug abuse.

(20) Abnormal pelvic type B ultrasonography finding that would contraindicate the use of triptorelin.

**Test product, dose, mode of administration:**

The test product is triptorelin pamoate PR 3-month formulation (triptorelin pamoate for injection 15 mg).

Triptorelin pamoate PR 3-month is a slightly yellow, freeze-dried cake or powder and solvent for suspension. For a single dose, the powder comprises triptorelin pamoate, D, L-lactide-coglycolide polymer, mannitol, sodium carmellose and polysorbate 80. The solvent provided for injection is a 2 mL ampoule of mannitol and water.

The product is administered by the intramuscular route only. The powder is reconstituted with the solvent provided and injected immediately after reconstitution. The product is administered as a single intramuscular injection every 12 weeks.

**Duration of treatment:** 24 weeks

**Reference therapy, dose and mode of administration:**

The comparator product is triptorelin acetate PR 1-month formulation (triptorelin acetate for injection 3.75 mg).

Triptorelin acetate PR 1-month is a practically white, freeze-dried cake or powder and solvent for suspension. For a single dose, the powder comprises triptorelin acetate, D, L-lactide-coglycolide polymer, mannitol, sodium carmellose and polysorbate 80. The solvent provided for injection is a 2 mL ampoule of mannitol and water.

This product is administered by the intramuscular route only. The powder is reconstituted with the solvent provided and injected immediately after reconstitution. The product is administered as a single intramuscular injection every 4 weeks.

**Criteria for evaluation:**

Efficacy:

Primary endpoint and evaluation:

- Percentage of subjects castrated ($E_2 \leq 184$ pmol/L or 50 pg/mL) at Week 12. The primary endpoint will be evaluated based on centralised bioanalysis of serum samples for $E_2$.

Secondary endpoints and evaluations:

- Percentage of subjects castrated ($E_2 \leq 184$ pmol/L or 50 pg/mL) at Weeks 4 and 8.
- Percentage of subjects castrated ($E_2 \leq 110$ pmol/L or 30 pg/mL) at Weeks 4, 8 and 12.
- Change in endometriosis-associated pelvic pain (by 10 cm VAS) at Weeks 4, 8 and 12 compared to baseline.
- $E_2$, FSH and LH concentrations at Weeks 4, 8 and 12.
- Time to menses recovery.

Pharmacokinetic/pharmacodynamic endpoints and evaluations:

A full triptorelin PK analysis will be conducted in a subgroup of up to 16 subjects in each treatment group (the full PK/PD subgroup: up to 32 subjects in total, to be enrolled at selected sites). Sparse PK samples will be taken in all subjects (in addition to the full PK subgroup) at Day 1 (baseline), and

Weeks 4, 8, 12 and 24. Additional hormone samples ($E_2$, FSH and LH) will be collected for PD assessments at Weeks 1, 2, 3 and 32 in the full PK/PD subgroup.

Noncompartmental analysis will only be performed on the PK data collected for the PK/PD subgroup to assess the PK parameters for the triptorelin pamoate PR 3-month and triptorelin acetate PR 1-month formulations. Population PK analysis (modelling) will be performed on PK data from all subjects.

Exploratory endpoints will include:

- Percentage of subjects castrated (as defined by both $E_2 \leq 184$ pmol/L (50 pg/mL) and $E_2 \leq 110$ pmol/L (30 pg/mL)) at Week 24;
- Change in endometriosis-associated pelvic pain (by 10 cm VAS) at Weeks 16, 20 and 24 and the end of study visit compared to baseline;
- Concentrations of $E_2$, FSH and LH at Week 24.
- The PK/PD relationship will be explored (PD markers being $E_2$, FSH and LH).

Safety:

Occurrence of adverse events (AEs) throughout the study, clinical laboratory (biochemistry, haematology and urinalysis) test results and electrocardiogram (ECG) findings at screening, Week 12 and Week 24, serum hormone ($E_2$, FSH and LH) concentrations at Week 40 (for those subjects whose menses do not recover at Week 40), vital signs (blood pressure and heart rate) measurements at each visit during treatment and end of study visit, physical/pelvic examination at screening, Week 12 and Week 24, pelvic type B ultrasound at screening (or within 1 month prior to screening), Week 12 (optional) and Week 24, and urinary pregnancy test at screening and baseline.

**Statistical methods:**

The analysis sets for the primary and secondary efficacy endpoints will be the full analysis set (FAS) and the per protocol (PP) set. If the lower limit of the 95% confidence interval (CI) of the difference in percentage of subjects castrated ($E_2 \leq 184$ pmol/L or 50 pg/mL) at Week 12 between the triptorelin pamoate PR 3-month and triptorelin acetate PR 1-month is >-10%, noninferiority of triptorelin pamoate PR 3-month will be confirmed.

For secondary endpoints relating to the percentage of subjects castrated (either $E_2 \leq 184$ pmol/L or $E_2 \leq 110$ pmol/L), the number and percentage of subjects will be presented by treatment group for each visit. The difference between the treatment groups will be calculated and displayed with the 95% CI. Raw values for serum concentrations of $E_2$, FSH and LH, endometriosis-associated pelvic pain (measured by VAS) and change from baseline, will be summarised, using number of available observations (n), mean, median, standard deviation (SD), and minimum and maximum values. For time to menses recovery, Kaplan-Meier curves, median time to event and 95% CIs will be provided.

Determination of sample size

The sample size was estimated based on data from Ipsen Study E-28-52014-705. Assuming the percentage of subjects castrated at Week 12 of triptorelin acetate PR 1-month treatment is no less than 92%, a sample size of 133 subjects in each treatment group will have 85% power to demonstrate the noninferiority of triptorelin pamoate PR 3-month to the comparator, when the lower limit of the 95% CI of the difference in percentage of subjects castrated at Week 12 between the treatment groups is >-10% and with a 0.025 one-sided type I error rate.

Assuming that the dropout rate will be around 10%, a sample size of 300 randomised subjects in total is planned for this study.

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# LIST OF ABBREVIATIONS

| ABBREVIATION | Wording Definition |
|---|---|
| **AE** | Adverse event |
| **$AUC_\tau$** | Area under the plasma concentration-time curve for the dosing interval |
| **CA** | Competent Authority |
| **CI** | Confidence interval |
| **$C_{max}$** | Maximum observed plasma concentration |
| **CMC-SC** | Chemistry, Manufacturing and Control-Supply Chain (relates to sponsor) |
| **$C_{min}$** | Minimum observed plasma concentration during the dosing interval |
| **CRO** | Contract research organisation |
| **CSR** | Clinical study report |
| **$E_2$** | Oestradiol |
| **ECG** | Electrocardiogram |
| **eCRF** | Electronic case report form |
| **EDC** | Electronic data capture |
| **EDTA** | Ethylenediaminetetracetic acid |
| **FAS** | Full analysis set |
| **FSH** | Follicle stimulating hormone |
| **GCP** | Good Clinical Practice |
| **GLP** | Good Laboratory Practice |
| **GnRH** | Gonadotrophin releasing hormone |
| **HCG** | Human chorionic gonadotrophin |
| **HIV** | Human immunodeficiency virus |
| **IB** | Investigator's brochure |
| **ICH** | International Conference on Harmonisation |
| **IEC** | Independent ethics committee |
| **IMP** | Investigational medicinal product |
| **IRB** | Institutional review board |
| **ISF** | Interim storage facility |
| **IWRS** | Interactive web response system |
| **LH** | Luteinising hormone |
| **MCH** | Mean corpuscular haemoglobin |
| **MCHC** | Mean corpuscular haemoglobin concentration |

| | |
|---|---|
| **MCV** | Mean corpuscular volume |
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **n** | Number of available observations |
| **NCA** | Noncompartmental analysis |
| **PD** | Pharmacodynamic(s) |
| **PDD** | Protocol deviation document |
| **PK** | Pharmacokinetic(s) |
| **PI** | Package insert |
| **PP** | Per protocol |
| **PR** | Prolonged release |
| **QTc** | Corrected QT interval |
| **RBC** | Red blood cell(s) |
| **SAE** | Serious adverse event |
| **SAP** | Statistical analysis plan |
| **SAS®** | Statistical Analysis System® |
| **SD** | Standard deviation |
| **SmPC** | Summary of product characteristics |
| **SOP** | Standard Operating Procedure |
| **TEAE** | Treatment-emergent adverse event |
| **TFL** | Tables, figures and listings |
| **$t_{max}$** | Time to maximum observed plasma concentration |
| **TMF** | Trial master file |
| **ULN** | Upper limit of normal |
| **VAS** | Visual analogue scale |
| **WBC** | White blood cell(s) |
| **WHO** | World Health Organisation |

# 1 BACKGROUND INFORMATION

## 1.1 Introduction

Endometriosis is a disorder experienced by approximately 7% to 10% of women. It is characterised by the presence of endometrial tissue fragments outside the uterine cavity, most commonly in the pelvic area. Endometriosis is an oestradiol ($E_2$) dependent disease and is relieved by the administration of antioestrogens, inhibitors of endogenous $E_2$ secretion, and by surgical oophorectomy or ectopic tissue surgery.

The disease may be asymptomatic, but where symptoms occur they usually consist of dysmenorrhoea, cyclical abdominal or pelvic pain, and dyspareunia. In addition, 30% to 40% of patients with endometriosis are infertile. This means that between 2% and 4% of women may be infertile due to endometriosis. Symptom intensity is not necessarily dependent upon the extent of the lesions and it is not unusual for endometriosis to be discovered in asymptomatic patients undergoing laparoscopy or laparotomy for some other reason. Since the symptomatology is also nonspecific, a diagnosis of endometriosis can only be confirmed by laparoscopy or other means that provide anatomical or histological evidence.

Treatment of endometriosis depends on a woman's symptoms, pregnancy plans, and age, as well as the extent of endometriosis. In some cases no treatment is necessary. Where treatment is required, two types are currently recommended, and these can be complementary. The first is surgery to remove the ectopic endometrial tissue. Furthermore, hormone treatment is used to suppress $E_2$ secretion, since $E_2$ stimulates the growth of endometrial tissue. The hypogonadotrophic state produced by hormonal suppressants reduces the menstrual flow and leads to apoptosis of the endometriotic lesions. The principal hormonal suppressants used are gonadotrophin releasing hormone (GnRH) agonists such as triptorelin.

The purpose of triptorelin treatment of endometriosis is symptomatic relief of the condition via suppression of $E_2$ production. The clinical effect is associated with reduction of $E_2$ levels to postmenopausal levels, and hence suppression of menses. The suppression of menses is known to reduce endometriotic deposits and improve clinical symptoms. At the present time, hormonal treatment can be used either as first-line treatment or in combination with surgery, particularly in cases of extensive endometriosis. The GnRH analogues are used either pre- or postoperatively.

## 1.2 Triptorelin

Triptorelin is a synthetic decapeptide analogue of natural GnRH, a hormone synthesised by the anterior and mediobasal hypothalamus that controls the synthesis and secretion of the gonadotrophins luteinising hormone (LH) and follicle stimulating hormone (FSH) [1]. Triptorelin is principally characterised by the substitution of the L-glycine at position 6 in the natural GnRH decapeptide with D-tryptophan, leading to increased duration of action and affinity for the pituitary receptor compared to the parent compound.

Binding of GnRH agonists to pituitary receptors is specific, saturable and reversible. The affinity of the agonist for these receptors is 100 times greater than that of the natural substance. At high concentrations and by continuous exposure, initially the agonist causes a transitory phase of hyperstimulation (flare-up) corresponding to a series of intracellular responses (phospholipase C pathway). Subsequently, the agonist causes a down-regulation of GnRH receptor number and a post-receptor desensitisation of the gonadotrophic cell, leading to reversible biochemical castration. Base concentrations of LH and FSH decrease, accompanied by suppression of response to stimulation by natural exogenous GnRH [2, 3].

Different triptorelin formulations are approved for use in China for a number of indications. Triptorelin acetate 3.75 mg prolonged release (PR) formulation (for monthly injections,

hereafter known as triptorelin acetate PR 1-month) is approved to treat endometriosis, as well as precocious puberty, prostate cancer, uterine fibromyomas and for use in female infertility as part of an in vitro fertilisation programme. This formulation, which is marketed in China as Diphereline 3.75 mg, represents the current standard of care in the management of endometriosis. In addition, a formulation for 3-monthly injections, triptorelin pamoate 15 mg PR formulation, hereafter referred to as triptorelin pamoate PR 3-month, is also approved for the treatment of prostate cancer only. This formulation, which is marketed in China as Triptorelin pamoate for injection 15 mg, is designed to deliver equivalent exposure to the 1-month formulation, without the need for monthly injections. This formulation is widely used to treat endometriosis in other territories.

A more detailed description of the product is given in Section 3.4. Further details may be found in the investigator's brochure (IB).

### 1.3 Findings from Clinical Studies

The efficacy of triptorelin in the treatment of endometriosis is well established [4]. Clinical studies have demonstrated rapid and sustained biochemical castration and improvement in the signs and symptoms of endometriosis. Consequently, various triptorelin formulations are approved for the treatment of endometriosis in different territories, including triptorelin acetate PR 1-month in China.

The pharmacodynamic (PD) and pharmacokinetic (PK) equivalence of triptorelin pamoate PR 3-month to triptorelin acetate PR 1-month with endometriosis was previously investigated in female European subjects in Ipsen Study E-28-52014-705 [5]. In this study, a total of 146 subjects received either a single dose of triptorelin pamoate PR 3-month (72 subjects) or triptorelin acetate PR 1-month (74 subjects) over 3 months. At 12 weeks, the efficacy of triptorelin pamoate PR 3-month (as determined by the percentage of subjects with $E_2$ concentrations suppressed to castration levels) was found to be noninferior to the 1-month formulation. Overall, 97% of subjects receiving triptorelin pamoate PR 3-month were castrated at Week 12, compared to 94% receiving the 1-month formulation.

Further details may be found in the IB.

### 1.4 Clinical Trial Rationale

This study will be conducted to support the use of a triptorelin pamoate PR 3-month formulation for the treatment of endometriosis in Chinese patients. The primary endpoint will be to demonstrate similar efficacy to the currently approved triptorelin 1-month formulation in terms of the proportion of subjects with $E_2$ concentrations suppressed to castration levels after 12 weeks.

### 1.5 Population to be Studied

The study will enrol adult female subjects with endometriosis who, in the judgement of the investigator, require 6 months' treatment with a GnRH agonist.

### 1.6 Compliance Statement

The study will be conducted in compliance with independent ethics committees/institutional review boards (IECs/IRBs), informed consent regulations, the Declaration of Helsinki and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. Any episode of noncompliance will be documented. In addition, the study will adhere to all local regulatory requirements.

Before initiating the study, the investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB for the study protocol/amendment(s), written informed consent form, any consent form updates, subject emergency study contact cards,

subject recruitment procedures (for example, advertisements), any written information to be provided to subjects and a statement from the IEC/IRB that they comply with GCP requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

# 2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES

## 2.1 Purpose of the Study

This phase III registration study will be conducted to evaluate the similar efficacy of two different formulations of triptorelin (triptorelin pamoate PR 3-month and triptorelin acetate PR 1-month) in Chinese subjects with endometriosis. Triptorelin acetate PR 1-month has been marketed in China since 1999 and is the current standard of care for endometriosis. Triptorelin pamoate PR 3-month is only approved to treat prostate cancer in China, but is widely used to treat endometriosis in other territories. The 3-month formulation combines the advantages of $E_2$ suppression with a longer duration of action, which increases the acceptability of treatment by limiting the number of injections required. This study will support the application for approval of triptorelin pamoate PR 3-month for the treatment of endometriosis in Chinese patients by demonstrating similar efficacy to the approved formulation, as well as an acceptable safety profile.

It is hypothesised that triptorelin pamoate PR 3-month will offer non-inferior efficacy to triptorelin acetate PR 1-month in the treatment of Chinese subjects with endometriosis (as previously demonstrated in a European population in Study E-28-52014-705 [5]).

## 2.2 Study Objectives

The primary objective of the study is to assess the efficacy of triptorelin pamoate PR 3-month formulation in Chinese female subjects with endometriosis by demonstrating the noninferiority of triptorelin pamoate PR 3-month formulation injected once as compared to triptorelin acetate PR 1-month formulation injected 3 times consecutively, assessed by the percentage of subjects castrated ($E_2 \leq 184$ pmol/L or 50 pg/mL) at Week 12.

The secondary objectives of the study are as follows:

- To assess other efficacy parameters including the percentage of subjects castrated at other time points, $E_2$, LH, and FSH concentrations, and the impact on endometriosis-associated pelvic pain.
- To assess the safety profile of triptorelin pamoate PR 3-month.
- To assess the PK of triptorelin pamoate PR 3-month and compare to triptorelin acetate PR 1-month.

The exploratory objectives of the study are:

- To assess efficacy parameters (percentage of subjects castrated, $E_2$, LH and FSH concentrations and impact on endometriosis-associated pelvic pain) after Week 12.
- To explore the PK/PD of triptorelin pamoate PR 3-month in a subset of subjects (PD markers being $E_2$, FSH and LH).

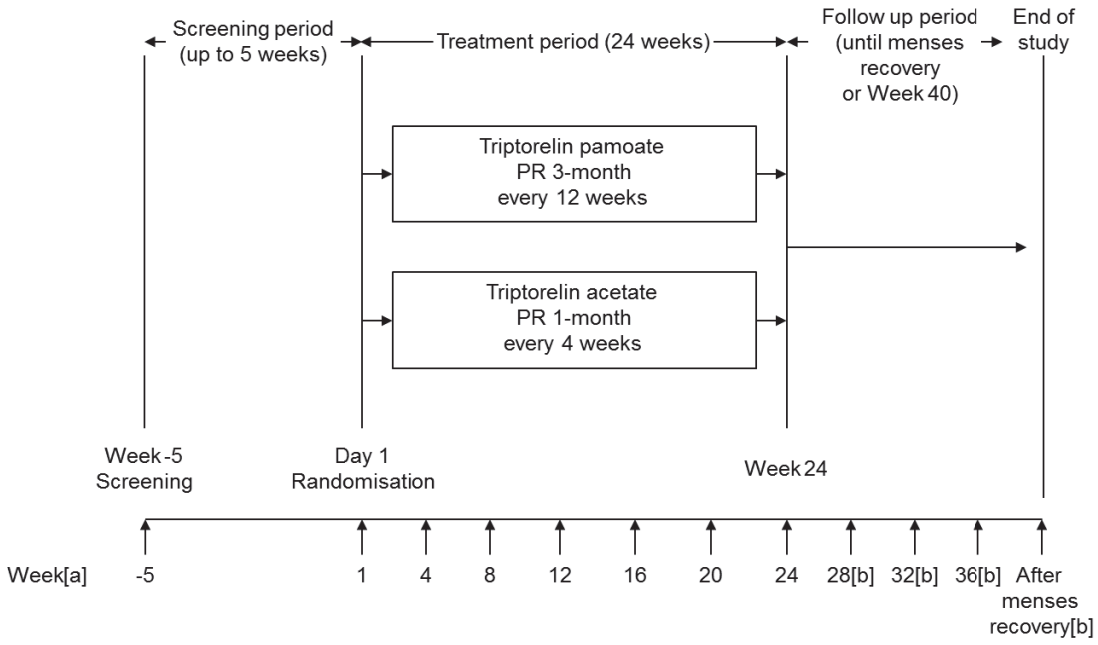
# 3 STUDY DESIGN

## 3.1 General Design and Study Schema

This is a prospective, phase III, multicentre, randomised, open-label, parallel group, active-controlled study. A total of 300 Chinese female subjects with endometriosis will be randomly assigned in a 1:1 ratio to triptorelin pamoate PR 3-month or triptorelin acetate PR 1-month. Specific details of the dosage groups are given in Section 6.

Subjects will be recruited and screened for eligibility up to 5 weeks prior to the first dose of investigational medicinal product (IMP) being administered. The first dose of IMP must be initiated at the baseline Visit (Day 1) in the follicular phase of subjects (the first to fifth day of the menses period). The treatment period will be 24 weeks, with the schedule of injections being once per 12 weeks for triptorelin pamoate PR 3-month (with subjects in this group receiving a total of two injections, one each at baseline and Week 12), or once per 4 weeks for triptorelin acetate PR 1-month (with subjects in this group receiving a total of six injections, one each at baseline and Weeks 4, 8, 12, 16 and 20). The subjects visit the study site every 4 weeks until Week 24, with the exception of the subgroup participating in the full PK and exploratory PD evaluations (up to 32 subjects, including up to 16 from each treatment group; to be enrolled at selected sites), who will have additional study visits. "Add back" treatment (recommended as, but not limited to, tibolone 2.5 mg once daily) may be administered after 12 weeks if needed based on the investigator's judgement. After 24 weeks' treatment, the subject will be followed up once every 4 weeks via telephone (except for subjects receiving triptorelin pamoate PR 3-month and participating in the full PK/PD subgroup, who will visit the study site) until menses recovery or Week 40 (whichever is earlier). The first visit after the menses recovery or Week 40 will be considered as the end of study visit. All subjects will attend the study site for the end of study visit. The principal study design features are summarised in Figure 1.

**Figure 1 Study Design**




[a] additional visits for subjects in the PK/PD subgroups not indicated
[b] during follow up, the first visit after menses recovery, or Week 40 (whichever is earlier) is considered the end of study visit

Treatment with GnRH agonists has been proven to be effective and well tolerated in patients suffering from endometriosis [5, 6, 7, 8, 9] with the mode of activity being mainly mediated

by $E_2$ suppression. Triptorelin acetate PR 1-month has been marketed in China since 1999, and represents the current standard of care in the management of endometriosis. As the active substance of triptorelin pamoate PR 3-month and triptorelin acetate PR 1-month is the same, and triptorelin has a proven mode of activity, it is justified to use $E_2$ suppression as the primary endpoint in this study to compare the efficacy and safety between both formulations.

According to Chinese guidelines, the recommended duration of GnRH agonist treatment for endometriosis is 3 to 6 months [10]. The duration of treatment in this study is therefore consistent with local treatment guidelines. In order to mitigate the potential for hypoestrogenaemia-related symptoms subjects can receive "add back" treatment from Week 12. Therefore, the primary efficacy endpoint will be assessed at Week 12. The additional 12 weeks of treatment is to allow the collection of additional efficacy and safety data.

As the appearance and the administration frequency of the two treatments are not identical, a double-blind study would have to include a "double-dummy" design, which would expose subjects to unnecessary additional injections. An open-label design has therefore been selected for this study. As the primary efficacy endpoint will be based on an objective laboratory parameter, which will be evaluated centrally, it is considered that the bias has been sufficiently minimised to support an open-label design.

## 3.2 Endpoints and Evaluations

### *3.2.1 Primary Efficacy Endpoint and Evaluation*

The percentage of subjects castrated ($E_2 \leq 184$ pmol/L or 50 pg/mL) at Week 12. The primary endpoint will be evaluated based on centralised bioanalysis of serum samples for $E_2$.

### *3.2.2 Secondary Efficacy Endpoints and Evaluations*

Secondary endpoints for this study include:

- Percentage of subjects castrated ($E_2 \leq 184$ pmol/L or 50 pg/mL) at Weeks 4 and 8.
- Percentage of subjects castrated ($E_2 \leq 110$ pmol/L or 30 pg/mL) at Weeks 4, 8 and 12.
- Change in endometriosis-associated pelvic pain (by 10 cm visual analogue scale (VAS)) at Weeks 4, 8 and 12 compared to baseline.
- $E_2$, FSH and LH concentrations at Weeks 4, 8 and 12.
- Time to menses recovery.

### *3.2.3 Pharmacokinetic/Pharmacodynamic Endpoints and Evaluations*

A full triptorelin PK analysis will be conducted in a subgroup of up to 16 subjects in each treatment group, to be enrolled at selected sites. Sparse PK samples will be taken in all subjects (in addition to the full PK/PD subgroup) at Day 1 (baseline), and Weeks 4, 8, 12 and 24. Additional hormone samples ($E_2$, FSH and LH) will be collected for PD assessments at Weeks 1, 2, 3 and 32 in the full PK/PD subgroup.

Noncompartmental analysis will only be performed on the PK data collected for the PK/PD subgroup to assess the PK parameters for the triptorelin pamoate PR 3-month and triptorelin acetate PR 1-month formulations. Population PK analysis (modelling) will be performed on PK data from all subjects.

### *3.2.4 Exploratory Efficacy Endpoints and Evaluations*

Exploratory endpoints for this study include:

- Percentage of subjects castrated (as defined by both $E_2 \leq 184$ pmol/L (50 pg/mL) and $E_2 \leq 110$ pmol/L (30 pg/mL)) at Week 24.
- Change in endometriosis-associated pelvic pain (by 10 cm VAS) at Weeks 16, 20 and 24 and the end of study visit compared to baseline.
- Concentrations of $E_2$, FSH and LH at Week 24.
- The PK/PD relationship will be explored (PD markers being $E_2$, FSH and LH).

### *3.2.5 Safety Endpoints and Evaluations*

The safety and tolerability of triptorelin will be assessed by evaluating the occurrence of adverse events (AEs) throughout the study, clinical laboratory parameters (biochemistry, haematology and urinalysis) test results and electrocardiogram (ECG) findings at screening, Week 12 and Week 24, serum hormone ($E_2$, FSH and LH) concentrations at Week 40 (for those subjects whose menses do not recover at Week 40), vital signs (blood pressure and heart rate) measurements at each visit during treatment and end of study visit, physical/pelvic examination at screening, Week 12 and Week 24, pelvic type B ultrasound at screening (or within 1 month prior to screening), Week 12 (optional) and Week 24, and urinary pregnancy test at screening and baseline.

## 3.3 Randomisation and Blinding

This is an open-label study, and there is no blinding. The sponsor's randomisation manager, a statistician independent from the study, will prepare the master randomisation list for this study. This list will be performed in blocks and will be based on a computer-generated randomisation list. It will be stratified according to endometriotic surgical history (previous or no previous surgery) and the severity of endometriosis-associated pelvic pain (VAS >3 or ≤3 cm), and will be generated with a balanced ratio (1 triptorelin pamoate PR 3-month to 1 triptorelin PR 1-month).

Subjects meeting the randomisation criteria will be allocated a randomisation number through an interactive web response system (IWRS) at baseline (Visit 2). This allocation will be performed in the order in which they enter the randomised study period and according to their endometriotic surgical history and severity of endometriosis-associated pelvic pain at baseline. The IWRS will assign subjects to one of two treatment groups based on a predefined randomisation list. A treatment number will be allocated by the IWRS each time drug is dispensed, according to the allocated treatment group. The IWRS will also manage all the logistical aspects of treatment (e.g. drug supplies; replacement of lost, damaged, quarantined, expiring or expired kits).

The investigator will under no circumstances change the randomisation number, the treatment number or the treatment arm allocated to the subject.

The IWRS will provide investigators, site coordinators and project team members with a 24-hour a day, 7-day a week service. Additional details may be found in the IWRS reference manual to be provided to each site. In case of technical, randomisation or dispensation queries, a 24-hour helpline will be available: see supporting information in the investigator site file.

Recruitment will stop once approximately 300 subjects have been randomised. Randomised subjects who terminate their study participation for any reason before starting the treatment will retain their randomisation number and treatment number (these numbers will not be reused). The next subject is given another randomisation number and another treatment number, even if she should receive the same treatment. Randomised subjects who leave the study early will not be replaced.

The sponsor's randomisation manager will keep the master randomisation list. A copy of this list will be confidentially supplied to the contract research organisation (CRO) in charge of the IWRS. The master list and the copy supplied to the CRO in charge of the IWRS will be kept confidential in a secure location. Access to the randomisation list must be restricted until authorisation is given to release it for final analysis.

### 3.4 Study Treatments and Dosage

The test product, triptorelin pamoate PR 3-month, will be administered as an intramuscular injection containing 15 mg triptorelin pamoate, once every 12 weeks. A more detailed description of administration procedures is given in Section 6.1.

The comparator is triptorelin acetate PR 1-month, the triptorelin formulation commercially approved for the treatment of endometriosis in China. The comparator will be administered as an intramuscular injection containing 3.75 mg triptorelin acetate, once every 4 weeks.

A more detailed description of administration procedures is given in Section 6.1.2.

The IMP will be packaged by Chemistry, Manufacturing and Control-Supply Chain (CMC-SC; Beaufour Ipsen Industrie, Rue Ethe Virton, 28100, Dreux, France) and delivered to the interim storage facility (ISF) in China, and then to study sites. A sufficient quantity of IMP will be supplied as well as an acknowledgement of receipt form.

The sponsor's representative will receive: a Certificate of Analysis for which batch of IMP has been used under their study and the Certificate of Compliance which reflects the product release statement.

The core label texts for all packaging units will be translated or adjusted, to be in compliance with applicable regulatory requirements, national laws in force and in accordance with the local languages. A description of the core text of the IMP labels is displayed below:

- Name, address and telephone number of the sponsor
- Study number
- Pharmaceutical dosage form
- Route of administration
- Quantity of dose units
- Batch number
- Treatment number
- Subject number/subject ID (this information will be completed by the investigator)
- "Keep out of reach of children"
- "For clinical trial use only"
- Storage conditions
- Expiry date

The investigator, or designee, will only dispense IMPs to subjects included in this study. Each subject will only be given the IMP carrying his/her number. The dispensing for each subject will be documented in the electronic case report form (eCRF).

### 3.5 Study Duration

This study will consist of a screening period of up to 5 weeks, a 24-week open-label treatment period and a follow up period of up to 16 weeks. The duration of the study is a minimum of 24 to 40 weeks, plus up to 5 weeks for the screening period.

The subject's participation in the study will be considered to have ended at the time of the last visit.

The overall duration of the study will be approximately 32 months, including approximately 21 months' recruitment. The study will be considered to have started when the first subject has been screened. The study will be considered to have ended after the last subject has completed the last visit in the study.

## 3.6 Stopping Rules and Discontinuation Criteria

There are no formal rules for early termination of this study. During the conduct of the study, serious adverse events (SAEs) will be reviewed (see Section 8.1.4) as they are reported from the study centre to identify any safety concerns. The study may be terminated by the sponsor at any time.

A subject may discontinue participation in the study at any time for any reason (for example, lack of efficacy, withdrawal of consent, AE). The investigator and/or sponsor can withdraw a subject from the study at any time for any reason (for example, protocol violation or deviation as defined in Section 12.1.2, noncompliance with the protocol conditions or AE).

## 3.7 Investigational Medicinal Product Preparation Storage and Accountability

### *3.7.1 Investigational Medicinal Product Storage and Security*

The investigator, or an approved representative (for example, pharmacist), will ensure that all IMP and any other study-related material is stored in a secured area, under recommended temperature-monitored storage conditions (below +25°C), in accordance with applicable regulatory requirements.

### *3.7.2 Investigational Medicinal Product Preparation*

The investigator, or an approved representative (for example, pharmacist), will ensure that all IMP is reconstituted and dispensed by qualified staff members.

### *3.7.3 Investigational Medicinal Product Accountability*

All IMP and any other study-related material is to be accounted for on the IMP accountability log provided by the sponsor. It is essential that all used and unused supplies are retained for verification (by the sponsor or sponsor's representative). The investigator should ensure adequate records are maintained in the IMP accountability log. The destruction of used and unused IMP should be carried out only after any discrepancies have been investigated and satisfactorily explained, and the reconciliation has been accepted. The IMP will be destroyed either on site or in the ISF.

## 3.8 Maintenance of Randomisation and Blinding

The investigator will under no circumstances change the randomisation number and the treatment arm allocated to the subject via the IWRS. As this is an open-label study, there is no blinding of investigator or subjects.

To mitigate any potential bias due to the open-label design of this study, $E_2$, LH and FSH concentrations will be evaluated centrally.

## 3.9 Source Data Recorded on the Case Report Form

Data will be collected in the eCRF in compliance with Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) Part 11. As required by GCP, the sponsor-assigned monitor will verify, by direct reference to the source documents, that the data required by the protocol are accurately reported on the eCRF.

The source documents must, as a minimum, contain a statement that the subject is included in a clinical study, the date that informed consent was obtained prior to participation in the study, the identity of the study, diagnosis and eligibility criteria, visit dates (with subject status), IMP administration details, and any AEs and associated concomitant medication.

As required by ICH GCP Section 6.4.9, if some items are recorded directly on the eCRF and are considered as source data, the identification of these data must be documented and agreed between the investigator and the sponsor.

Definition for source data and source documents are given below:

- **Source data**: All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
- **Source documents**: Original documents, data and records (for example, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x rays, subject files, and records kept at the pharmacy, at the laboratories and at medicotechnical departments involved in the clinical study).

The subject must have consented to their medical records being viewed by the sponsor's authorised personnel, and by local, and possibly foreign, competent authorities (CAs). This information is included in the informed consent.

# 4 SELECTION AND WITHDRAWAL OF SUBJECTS

## 4.1 Inclusion Criteria

All subjects must fulfil all of the following criteria to be included in the study:

(1) Female subjects aged from 18 to 45 years inclusive at the date of informed consent.

(2) Provided written informed consent.

(3) A history of active and regular menstrual cycles of 21 to 35 days (inclusive) in the 6 months prior to the screening visit.

(4) A diagnosis of endometriosis, confirmed by laparoscopy or laparotomy within 10 years prior to the screening visit.

(5) Requires treatment with a GnRH agonist for a period of 6 months in the judgement of the investigator.

(6) A negative pregnancy test prior to the start of treatment.

(7) Not at risk of pregnancy, i.e. subjects of childbearing potential must be actively using barrier contraception throughout the study treatment until menses resume.

## 4.2 Exclusion Criteria

Subjects will not be included in the study if any of the following criteria are met:

(1) Subject is menopausal.

(2) Subject is pregnant or lactating.

(3) A current history of undiagnosed abnormal genital bleeding.

(4) Received treatment with a GnRH agonist within 6 months prior to the screening visit.

(5) A history of hypersensitivity to GnRH agonists and/or any of the excipients.

(6) Received any other hormonal treatment within 3 months prior to the screening visit (oestrogens, progestogens, danazol, gestrinone and cyproterone acetate etc).

(7) Has been treated for endometriosis with traditional Chinese medicine within 1 month prior to screening.

(8) It is anticipated that the subject will require surgery during the study period.

(9) Chronic pelvic pain that is not caused by endometriosis, that would interfere with the assessment of endometriosis-associated pelvic pain.

(10) A significant endocrine disorder (except controlled diabetes mellitus).

(11) Known history of human immunodeficiency virus (HIV) infection.

(12) Known history of chronic active hepatitis, including viral hepatitis carriers (hepatitis B or hepatitis C).

(13) Clinically significant hepatic (any liver enzyme > 2× the upper limit of normal (ULN)) or renal (creatinine > ULN) abnormalities or any other dysfunction according to the investigator's judgement.

(14) Any psychiatric illness, severe or unstable known illness that in the investigator's opinion could affect the safety, conduct or outcome of the study.

(15) Use of concomitant therapy, which in the investigator's opinion may interfere with the evaluation of study treatment efficacy and safety.

(16) Treatment with any other experimental drug or device within 90 days prior to the screening visit and/or expectation of treatment with any other experimental drug or device during the conduct of the study.

(17) Any malignancy except curatively-treated basal cell skin cancer.

(18) Unable or unwilling to comply with the protocol.

(19) A history of alcohol and/or drug abuse.

(20) Abnormal pelvic type B ultrasonography finding that would contraindicate the use of triptorelin.

### 4.3 Subject Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki, each subject is free to withdraw from the study at any time. The investigator also has the right to withdraw a subject from the study in the event of concurrent illness, AEs, pregnancy (see Section 8.1.5), or other reasons concerning the health or wellbeing of the subject, or in the case of lack of cooperation. In addition, a subject may be withdrawn from the study as described in Sections 3.6, 6.2 and 8.1.7.

Should a subject decide to withdraw from the study after administration of the IMP, or should the investigator decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal should be made (see Section 5.2.4.4) and an explanation given of why the subject is withdrawing or being withdrawn from the study.

The reason for and date of withdrawal from the study must be recorded on the eCRF. If a subject withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an AE or a clinically significant laboratory test abnormality, monitoring will continue until the event has resolved or stabilised, until the subject is referred to the care of a local health care professional, or until a determination of a cause unrelated to the IMP or study procedure is made. The specific AE or test result(s) must be recorded on the eCRF. All evaluations should be performed, according to the protocol, on the last day the subject receives IMP, or as soon as possible thereafter.

# 5 STUDY PROCEDURES

## 5.1 Study Schedule

The schedule of procedures and assessments during the study is summarised in Table 2. Procedures and assessments specific to the PK and PD subgroups are summarised in Table 3 and Table 4.

**Table 2 Study Procedures and Assessments (All Subjects)**

| | Screening period | Treatment period | | | | | | | Follow up period [a] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 | Visit 8 | Visit 9 | Visit 10 | Visit 11 | End of study/early withdrawal visit |
| **Procedures and assessments** | **Screening up to -5 weeks** | **Baseline (1st to 5th day of menses)** | **Week 4** | **Week 8** | **Week 12** | **Week 16** | **Week 20** | **Week 24** | **Week 28** | **Week 32** | **Week 36** | **Within 15 days after menses recovery or Week 40[b] (Day 281±3 days)** |
| **Visit window (days)** | **-35 to -1** | **Day 1** | **Day 29 ±3** | **Day 57 ±3** | **Day 85 ±3** | **Day 113 ±3** | **Day 141 ±3** | **Day 169 ±3** | **Day 197 ±3** | **Day 225 ±3** | **Day 253 ±3** | |
| Informed consent | X | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | |
| Significant medical or surgical history | X | | | | | | | | | | | |
| Prior medications for endometriosis | X | | | | | | | | | | | |
| Inclusion and exclusion criteria | X | X | | | | | | | | | | |
| $E_2$, FSH and LH | | X[c] | X[c] | X[c] | X[c] | | | X | | | | X[d] |
| VAS | | X | X | X | X | X | X | X | | | | X |
| Physical examination[e] | X | | | | X | | | X | | | | |
| Pelvic examination | X | | | | X | | | X | | | | |
| Vital signs | X | X | X | X | X | X | X | X | | | | X |
| Blood biochemistry[f] | X | | | | X | | | X | | | | |
| Haematology[f] | X | | | | X | | | X | | | | |
| Urinalysis[f] | X | | | | X | | | X | | | | |
| Urine pregnancy test | X | X | | | | | | | | | | |
| 12-lead ECG | X | | | | X | | | X | | | | |
| Pelvic type B ultrasound scan | X[g] | | | | X[h] | | | X | | | | |
| Sparse PK assessments | | X[c] | X[c] | X[c] | X[c] | | | X | | | | |
| Randomisation | | X | | | | | | | | | | |
| Study drug injection (3-month formulation) | | X[i] | | | X | | | | | | | |
| Study drug injection (1-month formulation) | | X[i] | X | X | X | X | X | | | | | |
| AEs | X | X | X | X | X | X | X | X | X | X | X | X |

**Table 2 Study Procedures and Assessments (All Subjects)**

| | Screening period | Treatment period | | | | | | | Follow up period [a] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 | Visit 8 | Visit 9 | Visit 10 | Visit 11 | End of study/early withdrawal visit |
| **Procedures and assessments** | **Screening up to -5 weeks** | **Baseline** | **Week 4** | **Week 8** | **Week 12** | **Week 16** | **Week 20** | **Week 24** | **Week 28** | **Week 32** | **Week 36** | **Within 15 days after menses recovery or Week 40[b] (Day 281±3 days)** |
| **Visit window (days)** | **-35 to -1** | **Day 1** | **Day 29 ±3** | **Day 57 ±3** | **Day 85 ±3** | **Day 113 ±3** | **Day 141 ±3** | **Day 169 ±3** | **Day 197 ±3** | **Day 225 ±3** | **Day 253 ±3** | |
| Prior and concomitant medication/therapies | X | X | X | X | X[j] | X[j] | X[j] | X | X | X | X | X |
| Status of menses | X | X | X | X | X | X | X | X | X | X | X | X |

AE=adverse event; $E_2$=oestradiol; ECG=electrocardiogram; FSH=follicle stimulation hormone; LH=luteinising hormone; PK=pharmacokinetic; VAS=visual analogue scale

a during the follow up period, the first visit after menses recovery, or Week 40 (whichever is earlier) will be considered the final visit (end of study). The end of study visit should be a clinic visit. Follow up visits prior to the end of study visit will be telephone contact visits

b or upon early withdrawal from the study

c samples taken predose, where applicable

d only if subject's menses do not recover before Week 40

e subject height and weight will be assessed at screening only

f samples for clinical laboratory testing will be taken after at least 8 hours fasting

g a result within 1 month prior to the screening visit will be acceptable

h optional, based on the subject's disease condition, as judged by the investigator

i study treatment must be initiated during the subject's follicular phase (first to fifth day of menses period)

j from Week 12, after the primary endpoint evaluation, "add back" treatment will be permitted if needed according to the investigator's judgement. "Add back" treatment will be recommended as, but not limited to, tibolone 2.5 mg once daily

**Table 3 Full PK/PD Assessments Day 1 to Week 12 (PK/PD Subgroup Subjects)**

| Assessment[a] | Treatment period | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day 1 | Week 1 (hours post Day 1 dosing) | | | Week 2 | Week 3 | Week 4 | Week 6 | Week 8 | Week 10 | Week 12 |
| **Assessment time (study day/hours postdose)[b]** | **Day 1** | **24** | **48** | **168** | **Day 15** | **Day 22** | **Day 29** | **Day 43** | **Day 57** | **Day 71** | **Day 85** |
| PK (3M) | X[c] | X | X | X | X | X | X | X | X | | X[c] |
| PK (1M) | X[c] | X | X | X | X | X | X[d] | | X[d] | X | X[d] |
| PD ($E_2$, FSH and LH) | | | | X | X | X | | | | | |
| AEs | X | X | | | X | X | X | X | X | X | X |
| Prior and concomitant medication/therapies | X | X | | | X | X | X | X | X | X | X |

1M=triptorelin acetate PR 1-month; 3M=triptorelin pamoate PR 3-month; AE=adverse event; $E_2$=oestradiol; FSH=follicle stimulating hormone; LH=luteinising hormone; PD=pharmacodynamics; PK=pharmacokinetics.

a assessments to be conducted with samples from the subjects in the full PK/PD subgroup (comprising up to 16 subjects receiving 3M and up to 16 subjects receiving 1M; to be enrolled at selected sites)

b time windows for full PK/PD assessments will be defined in the Study Manual

c samples taken predose and 0.5, 1, 2, 4, 8 and 12 hours postdose

d samples taken predose

**Table 4 Full PK/PD Assessments Week 13 to End of Study (PK/PD Subgroup Subjects)**

| Assessment[a] | Treatment period | | | | | | | | | Follow up period | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Week 13 (hours post Week 12 dosing) | | | Week 14 | Week 15 | Week 16 | Week 18 | Week 20 | Week 24 | Week 28 | Week 32 | Week 36 | End of study/ early withdrawal |
| **Assessment time (study day/hours postdose)[b]** | **24** | **48** | **168** | **Day 99** | **Day 106** | **Day 113** | **Day 127** | **Day 141** | **Day 169** | **Day 197** | **Day 225** | **Day 253** | **See Table 2** |
| PK (3M) | X | X | X | X | X | X | X | X | X | X | X | X | |
| PK (1M) | | | | | | | | | X | X | X | X | |
| PD ($E_2$, FSH and LH) | | | | | | | | | | | X | | |
| AEs | X | | | X | X | X | X | X | X | X | X | X | X |
| Prior and concomitant medication/therapies | X | | | X | X | X | X | X | X | X | X | X | X |

1M=triptorelin acetate PR 1-month; 3M=triptorelin pamoate PR 3-month; AE=adverse event; $E_2$=oestradiol; FSH=follicle stimulating hormone; LH=luteinising hormone; PD=pharmacodynamics; PK=pharmacokinetics.

a assessments to be conducted with samples from the subjects in the full PK/PD subgroup (comprising up to 16 subjects receiving 3M and up to 16 subjects receiving 1M; to be enrolled at selected sites) only

b time windows for full PK/PD assessments will be defined in the Study Manual

The total volume of blood drawn for all evaluations throughout this study for each subject not in the full PK/PD subgroup will be approximately 47.5 mL (Table 5).

Additional blood samples for subjects in the full PK/PD subgroup are presented in Table 6. The total volume of blood drawn (including blood samples taken from all subjects, and additional PK/PD samples) will be 121.5 mL for subjects receiving triptorelin pamoate 3-month and 93.5 mL for subjects receiving triptorelin acetate 1-month.

**Table 5 Blood Volume Calculation (All Subjects)**

| Description | Number of samples | Volume (mL) | Total volume (mL) |
|---|---|---|---|
| Haematology | 3 | 2 | 6 |
| Blood biochemistry | 3 | 2.5 | 7.5 |
| $E_2$, FSH and LH | 6 | 4 | 24 |
| Sparse PK | 5 | 2 | 10 |
| Total volume (mL) | | | 47.5 |

$E_2$=oestradiol; FSH=follicle stimulating hormone; LH=luteinising hormone; PK=pharmacokinetics.

**Table 6 Additional Blood Samples (Full PK/PD Subgroup)**

| Description | Number of samples | Volume (mL) | Total volume (mL) |
|---|---|---|---|
| **Subjects receiving triptorelin pamoate 3-month** | | | |
| $E_2$, FSH and LH | 4 | 4 | 16 |
| PK | 29 | 2 | 58 |
| Total volume (mL) | | | 74 |
| **Subjects receiving triptorelin acetate 1-month** | | | |
| $E_2$, FSH and LH | 4 | 4 | 16 |
| PK | 15 | 2 | 30 |
| Total volume (mL) | | | 46 |

$E_2$=oestradiol; FSH=follicle stimulating hormone; LH=luteinising hormone; PD=pharmacodynamics; PK=pharmacokinetics.

## 5.2 Study Visits

### *5.2.1 Procedures for Screening and Enrolment (Visit 1; up to -5 weeks)*

A signed and dated informed consent form will be obtained before screening procedures. Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the study specific evaluations. Subjects will acknowledge and agree to the possible use of this information for the study by giving informed consent.

After informed consent is obtained, subjects who are screened will be allocated a subject number. All screened subjects must be identifiable throughout the study. The investigator will maintain a list of subject numbers and names to enable records to be found at a later date if required.

Rescreening will not be permitted in this study.

The screening visit (Visit 1) will take place up to 5 weeks prior to the first dose of IMP being administered. The following assessments will be performed at screening:

- Demographic data (date of birth, sex, ethnicity, and race)
- Significant medical or surgical history, including ongoing medical conditions, AEs, gynaecological history, date of last menses
- Eligibility check (inclusion/exclusion criteria)
- Physical examination (including subject height and body weight)
- Pelvic examination
- Vital signs (sitting blood pressure and heart rate)
- Laboratory safety tests (blood sampling for biochemistry, haematology and urinalysis)

- Urine pregnancy test, method of contraception
- 12-lead ECG
- Pelvic type-B ultrasound scan (a result obtained within 1 month of the screening visit will be acceptable)
- Prior and concomitant medications/therapies (including medications and therapies for endometriosis)
- Record date of onset of last menses and expected date of onset of next menses

Each investigator will also maintain a record of all subjects screened into the study (i.e. who signed the informed consent form). Records up to the time of premature subject termination should be completed and the primary reason for termination will be recorded.

### *5.2.2 Procedures before Study Treatment (Baseline, Visit 2 Predose)*

Subjects will be instructed to contact the study centre by telephone at the onset of their menses period to arrange their baseline visit (Visit 2, Day 1), which must occur in the follicular phase (from the first to the fifth day of menses). Administration of study treatment will be initiated at the baseline visit, following randomisation to one of the two treatment groups, as specified in Section 6.1. The following procedures will be performed at baseline on Day 1 of the study, prior to administration of study treatment:

- Urine pregnancy test
- Baseline efficacy assessments ($E_2$, LH and FSH concentrations; VAS)
- Samples taken for sparse PK analysis
- Vital signs
- Review of pretreatment AEs
- Prior and concomitant medications/therapies
- Date of onset of menses, current menses status
- Eligibility check (inclusion/exclusion criteria)
- Randomisation
- Allocation to the full PK/PD subgroup (selected sites only)

#### *5.2.2.1 Pharmacokinetic Blood Sampling*

Predose samples, as described in Section 5.2.2, will be the same for the full PK/PD subgroup and the sparse PK analysis. No additional predose samples are planned.

### *5.2.3 Procedures during Study Treatment (Visit 2 Postdose to Visit 8)*

Subjects receiving triptorelin acetate PR 1-month will receive study drug at each visit during the treatment period up to and including Visit 7 (Week 20, Day 141±3). Subjects receiving triptorelin pamoate PR 3-month will receive study drug at Visit 2 (Day 1) and Visit 5 (Week 12, Day 85±3) only.

The following procedures will be performed on all subjects at Visit 3 (Week 4, Day 29±3) and Visit 4 (Week 8, Day 57±3):

- Efficacy assessments ($E_2$, LH and FSH concentrations (samples taken predose for subjects receiving triptorelin acetate PR 1-month); VAS)
- Samples taken for sparse PK analysis (samples taken predose for subjects receiving triptorelin acetate PR 1-month)
- Vital signs
- Review of AEs

- New or changed concomitant medications/therapies
- Review of menses status and record date of menses onset (if applicable)
- Injection of IMP (subjects receiving triptorelin acetate PR 1-month only)

The following procedures will be performed at Visit 5 (Week 12, Day 85±3):

- Efficacy assessments ($E_2$, LH and FSH concentrations (samples taken predose for all subjects); VAS)
- Samples taken for sparse PK analysis (samples taken predose for all subjects)
- Physical examination
- Pelvic examination
- Vital signs
- Laboratory safety tests (blood sampling for biochemistry, haematology and urinalysis)
- 12-lead ECG
- Pelvic type B ultrasound scan (optional based on subject's disease condition, as judged by the investigator)
- Review of AEs
- New or changed concomitant medications, including details of any "add back" therapy
- Review of menses status and record date of menses onset (if applicable)
- Injection of IMP (all subjects)

The following procedures will be performed at Visit 6 (Week 16, Day 113±3) and Visit 7 (Week 20, Day 141±3):

- VAS assessment
- Vital signs
- Review of AEs
- New or changed concomitant medications/therapies, including details of any "add back" therapy
- Review of menses status and record date of menses onset (if applicable)
- Injection of IMP (subjects receiving triptorelin acetate PR 1-month only)

The following procedures will be performed at Visit 8 (Week 24, Day 169±3):

- Efficacy assessments ($E_2$, LH and FSH concentrations; VAS)
- Physical examination
- Pelvic examination
- Vital signs
- Laboratory safety tests (blood sampling for biochemistry, haematology and urinalysis)
- 12-lead ECG
- Pelvic type B ultrasound scan
- Samples taken for sparse PK analysis
- Review of AEs
- New or changed concomitant medications/therapies, including details of any "add back" therapy

- Review of menses status and record date of menses onset (if applicable)

*5.2.3.1 Full Pharmacokinetic Blood Sampling during Treatment*

***Triptorelin Pamoate PR 3-month***

The full PK/PD subgroup will include up to 16 subjects receiving triptorelin pamoate PR 3-month. These subjects will attend the study centre for additional PK blood sampling at the following timepoints during the treatment period:

- Visit 2, Day 1 (0.5, 1, 2, 4, 8 and 12 hours postdose)
- Week 1 (24, 48 and 168 hours postdose)
- Week 2 (Day 15)
- Week 3 (Day 22)
- Week 6 (Day 43)
- Visit 5, Week 12 (Day 85, corresponding to the second administration of triptorelin pamoate PR 3-month): 0.5, 1, 2, 4, 8 and 12 hours postdose
- Week 13 (24, 48 and 168 hours postdose)
- Week 14 (Day 99)
- Week 15 (Day 106)
- Visit 6, Week 16 (Day 113)
- Week 18 (Day 127)
- Visit 7, Week 20 (Day 141)

In addition, at each visit, changes to ongoing and new AEs and concomitant medications and therapies will be recorded. Note that these PK blood samples are in addition to those described in Section 5.2.3.

***Triptorelin Acetate PR 1-month***

The full PK/PD subgroup will include up to 16 subjects receiving triptorelin acetate PR 1-month. These subjects will attend the study centre for additional PK blood sampling at the following timepoints during the treatment period:

- Visit 2, Day 1 (0.5, 1, 2, 4, 8 and 12 hours postdose)
- Week 1 (24, 48 and 168 hours postdose)
- Week 2 (Day 15)
- Week 3 (Day 22)
- Week 10 (Day 71)

In addition, at each visit, changes to ongoing and new AEs and concomitant medications and therapies will be recorded. Note that these PK blood samples are in addition to those described in Section 5.2.3.

*5.2.3.2 Full Pharmacodynamic Assessments*

The full PK/PD subgroup will comprise up to 32 subjects (up to 16 subjects from each treatment group; to be enrolled at selected sites). All subjects in the full PK/PD subgroup (both treatment groups) will attend the study centre for additional PD efficacy assessments ($E_2$, LH and FSH concentrations) at the following timepoints during the treatment period:

- Week 1 (Day 8)
- Week 2 (Day 15)
- Week 3 (Day 22)

### *5.2.4 Procedures during Follow Up Period (Visit 9 to End of Study)*

The purpose of the follow up period is to monitor menses recovery. Visits 9, 10 and 11 (Weeks 28, 32 and 36) will be conducted by telephone, primarily to establish if subjects' menses have recovered. If menses recover during the follow up period, subjects should attend the study site within 15 days after the first day of menses recovery. If there is no menses recovery by Week 40, the subject should attend the study site at Week 40 (Day 281±3). The first visit after menses recovery, or Week 40 (whichever is earlier) will be considered the end of study visit (see Section 5.2.4.4).

#### *5.2.4.1 Follow Up Visits to be Conducted by Telephone*

The following procedures will be performed by telephone at Visit 9 (Week 28, Day 197±3), Visit 10 (Week 32, Day 225±3) and Visit 11 (Week 36, Day 253±3) if required:

- Review of AEs
- New or changed concomitant medications/therapies
- Review of menses recovery status and record date of menses onset (if applicable)

#### *5.2.4.2 Full Pharmacokinetic Blood Sampling during Follow Up*

Subjects included in the full PK/PD subgroup will attend the study centre for PK blood sampling at the following timepoints during the follow up period:

- Visit 9, Week 28 (Day 197)
- Visit 10, Week 32 (Day 225)
- Visit 11, Week 36 (Day 253)

Note that subjects included in the full PK/PD subgroup will be required to attend full PK sampling visits during the follow up period, even if their menses recover prior to Week 40.

#### *5.2.4.3 Full Pharmacodynamic Assessments during Follow Up*

Subjects included in the full PK/PD subgroup will have an additional PD blood sample at Visit 10, Week 32 (Day 225).

Note that subjects included in the full PK/PD subgroup will be required to attend this PD sampling visit during the follow up period, even if their menses recover prior to Week 40.

#### *5.2.4.4 End of Study Visit or Early Withdrawal Visit*

The end of study visit will be the first visit within 15 days after the first day of menses recovery, or at Week 40 (Day 281±3), whichever is earlier. Subjects who withdraw from the study early will also attend an end of study visit.

Subjects who participate in the study in compliance with the protocol for 24 weeks of study drug administration will be considered to have completed study treatment. Subjects who participate in the study in compliance with the protocol for the 24 weeks of study drug administration, and complete the follow up period, will be considered to have completed the study.

For subjects who complete the study, or for those who withdraw prematurely from the study, final evaluations will be performed on the last day the subject receives the study drug, or as soon as possible afterwards. Subjects with ongoing AEs or clinically significant laboratory test abnormalities (as determined by the investigator) will be monitored as described in Section 8.1.3 and Section 8.1.2.4, respectively.

The following procedures will be performed at the end of study visit:

- $E_2$, LH and FSH concentrations (only if the subject's menses does not recover before Week 40)

- VAS assessment
- Vital signs
- Review of AEs
- New or changed concomitant medications/therapies
- Review of menses recovery status and record the date of menses onset (if applicable)

# 6 TREATMENT OF SUBJECTS

## 6.1 Study Drugs Administered

At screening, subjects will be allocated a subject number. Following confirmation of eligibility for the study at baseline (Visit 2, Day 1), subjects will be allocated a randomisation number, and assigned to one of the following treatment groups:

- triptorelin pamoate PR 3-month, administered as an intramuscular injection once every 12 weeks (a total of 2 injections).

or

- triptorelin acetate PR 1-month, administered as an intramuscular injection once every 4 weeks (a total of 6 injections).

### *6.1.1 Triptorelin Pamoate PR 3-month*

The test product is triptorelin pamoate PR 3-month, which comprises microparticles with the active ingredient incorporated in the copolymer. The product is presented as a slightly yellow freeze-dried cake or powder containing triptorelin pamoate; D, L-lactide-coglycolide polymer, mannitol, sodium carmellose and polysorbate 80. The solvent provided for injection is a 2 mL ampoule of mannitol and water. This product is marketed in China as Triptorelin pamoate for injection 15 mg, for the treatment of prostate cancer only.

Triptorelin pamoate PR 3-month is to be administered by the intramuscular route only. The powder is reconstituted with the solvent provided and injected immediately after reconstitution. The product is administered as a single intramuscular injection every 12 weeks (Day 1 and Week 12), as indicated in Table 2.

### *6.1.2 Triptorelin Acetate PR 1-month*

The comparator product is triptorelin acetate PR 1-month, which is formulated as microparticles. The comparator is presented as a practically white, freeze-dried cake or powder containing triptorelin acetate; D, L-lactide-coglycolide polymer, mannitol, sodium carmellose and polysorbate 80. The solvent provided for injection is a 2 mL ampoule of mannitol and water. This product is marketed in China as Diphereline 3.75 mg for various indications including the treatment of endometriosis.

Triptorelin acetate PR 1-month is to be administered by the intramuscular route only. The powder is reconstituted with the solvent provided and injected immediately after reconstitution. The product is administered as a single intramuscular injection every 4 weeks (Day 1 and Weeks 4, 8, 12, 16 and 20) as indicated in Table 2.

## 6.2 Concomitant Medication/Therapy

Any prior or concomitant therapy or medication given to a subject within 6 months prior to screening or during the study will be indicated on the eCRF. Dose and generic name or tradename will be indicated.

The following concomitant therapies or medications will not be permitted during the study:

- GnRH agonists other than the IMP.
- Other hormonal treatments (for example oestrogens, progestogens, danazol, gerstrinone, cyproterone acetate, and non-barrier contraception, etc).
- Surgery.
- Any concomitant therapies which, in the investigator's opinion, may interfere with the evaluation of study treatment efficacy and safety.
- Any experimental drug or device other than the IMP.

- Traditional Chinese medicine for the treatment of endometriosis.

As the primary endpoint will be assessed at Week 12, "add back" treatment will not be permitted before that time. If "add back" treatment is needed, according to the investigator's judgement, it can be initiated after the primary endpoint evaluation at Week 12. The reason for and date/time of all doses of "add back" treatment will be recorded in the eCRF. "Add back" treatment is recommended to be, but not limited to, tibolone at a dose of 2.5 mg once daily.

## 6.3 Procedures for Monitoring Subject Compliance

The investigator will be responsible for monitoring subject compliance. Subjects can be withdrawn from the study at any time if the investigator or the sponsor determines that the subject is not in compliance with the study protocol.

For this study, all doses of IMP will be administered to the subjects at the study centre by study site staff. Administration of IMP must occur at the study day indicated ±3 days. Administration compliance will be assessed by comparing the number of doses expected with the number of doses administered. Any missing injection at Visits 2, 3 or 4 (Day 1, Week 4 or Week 8) will be regarded as a major protocol violation.

Where a subject is consistently noncompliant with IMP intake they should be discontinued from IMP/withdrawn from the study. Please refer to Section 4.3 for the criteria for discontinuing the subject from IMP.

# 7 ASSESSMENT OF EFFICACY

For the timing of assessments in this study, refer to the schedule in Table 2.

## 7.1 Primary Efficacy Endpoint and Evaluation

The primary efficacy endpoint is the percentage of subjects castrated ($E_2 \leq 184$ pmol/L or 50 pg/mL) at Week 12. The primary endpoint will be evaluated based on centralised bioanalysis of serum samples for $E_2$.

## 7.2 Secondary and Exploratory Efficacy Endpoints and Evaluations

Secondary and exploratory efficacy endpoints and evaluations are summarised in Table 7.

**Table 7 Secondary and Exploratory Efficacy Endpoints and Evaluations**

| Measure | Timepoint | Variable | Endpoint |
|---|---|---|---|
| $E_2$ concentration | Baseline, Weeks 4, 8, 12 and 24 | Castration rate (percentage of subjects with $E_2$ below castration levels)<br>$E_2$ concentration | Secondary endpoints<br>Percentage of subjects castrated ($E_2 \leq 184$ pmol/L or 50 pg/mL) at Weeks 4 and 8.<br>Percentage of subjects castrated ($E_2 \leq 110$ pmol/L or 30 pg/mL) at Weeks 4, 8 and 12.<br>$E_2$ concentration at Weeks 4, 8 and 12.<br>Exploratory endpoints<br>Percentage of subjects castrated ($E_2 \leq 184$ pmol/L or 50 pg/mL) at Week 24.<br>Percentage of subjects castrated ($E_2 \leq 110$ pmol/L or 30 pg/mL) at Week 24.<br>$E_2$ concentration at Week 24. |
| Endometriosis-associated pelvic pain (by 10 cm VAS) | Baseline, Weeks 4, 8, 12, 16, 20, 24 and end of study/early withdrawal | Change in endometriosis-associated pelvic pain | Secondary endpoint<br>Change in endometriosis-associated pelvic pain (by 10 cm VAS) at Weeks 4, 8 and 12 compared to baseline.<br>Exploratory endpoint<br>Change in endometriosis-associated pelvic pain (by 10 cm VAS) at Weeks 16, 20, 24 and the end of study visit compared to baseline. |
| FSH and LH concentrations | Baseline, Weeks 4, 8, 12 and 24 | FSH concentration<br>LH concentration | Secondary endpoint<br>FSH and LH concentrations at Weeks 4, 8 and 12.<br>Exploratory endpoint<br>FSH and LH concentrations at Week 24. |
| Menses recovery | Baseline, date of first observation of menstrual bleeding at Weeks 28, 32, 36 and end of study/early withdrawal | Time to menses recovery | Secondary endpoint<br>Time to menses recovery. |

$E_2$=oestradiol; FSH=follicle stimulating hormone; LH=luteinising hormone; VAS=visual analogue scale.

## 7.3 Methods and Timing of Assessing, Recording, and Analysing Efficacy Data

The methods for assessing efficacy data are described below, and the timing of efficacy assessments is discussed in Section 5. Procedures for recording efficacy data are discussed in Section 14.1, and methods of analyses are discussed in Section 10.4.6.

### *7.3.1 Oestradiol, Follicle Stimulating Hormone and Luteinising Hormone Concentrations*

Assessments of serum $E_2$, FSH and LH concentrations will be performed at study visits at Day 1 (baseline) and Weeks 4, 8, 12 and 24, in accordance with Table 2. A further assessment will be conducted at Week 40 in subjects whose menses have not recovered by this timepoint. This assessment is considered a safety assessment, and is discussed in Section 8.2.5. In addition, serum $E_2$, FSH and LH concentrations will also be determined at Weeks 1, 2, 3 and 32 for subjects in the full PK/PD subgroup, as described in Section 9.2. All $E_2$, FSH and LH concentrations will be evaluated by the central laboratory.

#### *7.3.1.1 Oestradiol Concentrations*

Measurement of serum $E_2$ concentrations will be performed in a central laboratory in accordance with Good Laboratory Practice (GLP). All details of the sample collection, handling, shipment, methodology and reference ranges will be provided in the Study Manual and archived in the trial master file (TMF).

Castration rate will be assessed using a cutoff $E_2$ concentration of 184 pmol/L (50 pg/mL) for the primary and secondary efficacy endpoints, and 110 pmol/L (30 pg/mL) for the secondary efficacy endpoint only.

#### *7.3.1.2 Luteinising Hormone and Follicle Stimulating Hormone Concentrations*

Measurement of serum LH and FSH concentrations will be performed in a central laboratory in accordance with GLP. All details of the sample collection, handling, shipment, methodology and reference ranges will be provided in the Study Manual and archived in the TMF.

### *7.3.2 Endometriosis-associated Pelvic Pain*

The severity of endometriosis-associated pain will be assessed by the subject at Day 1 (baseline), Weeks 4, 8, 12, 16, 20, 24, and at the end of study visit using a 10 cm VAS. Subjects will be asked to assess their most severe endometriosis-associated pain over the preceding 4 weeks. For the Day 1 (baseline) assessment, if subjects had undergone endometriotic surgery within the previous 4 weeks, they will be asked to assess their most severe endometriosis-associated pain postsurgery. The VAS to be used is presented in Appendix 1.

### *7.3.3 Recovery of Menses*

Status of menses recovery will be assessed at all study visits, including the follow-up period (Weeks 28, 32, 36 and at the end of study visit). The date of menses (if available) will be recorded at the end of study visit. Time to menses recovery will be defined as the time (in days) between the date of the last dose of study drug and the date of the first day that the subject observed menstrual bleeding of the next menses period. Any subjects withdrawing from the study without menstrual bleeding will be censored in this analysis at the date of withdrawal. Any subjects without menstrual bleeding prior to the end of study visit will be censored in this analysis at the date of the end of study visit.

# 8 ASSESSMENT OF SAFETY

## 8.1 Adverse Events

Adverse events will be monitored from the time that the subject gives informed consent and throughout the study (see Section 3.5 for a definition of the study duration) and will be elicited by direct, nonleading questioning or by spontaneous reports. Further details for AE reporting can be found in Section 8.1.2.

### *8.1.1 Definition of an Adverse Event*

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (for example, nausea, chest pain), signs (for example, tachycardia, enlarged liver) or the abnormal results of an investigation (for example, laboratory findings, ECG). In clinical studies an AE can include an undesirable medical condition occurring at any time, including run in or washout periods, even if no IMP has been administered.

This definition includes events occurring from the time of the subject giving informed consent until the end of the study (as defined in Section 3.5).

### *8.1.2 Categorisation of Adverse Events*

#### *8.1.2.1 Intensity Classification*

Adverse events will be classified as mild, moderate or severe according to the following criteria:

- **Mild:** symptoms do not alter the subject's normal functioning
- **Moderate:** symptoms produce some degree of impairment to function, but are not hazardous, uncomfortable or embarrassing to the subject
- **Severe:** symptoms definitely hazardous to wellbeing, significant impairment of function or incapacitation.

#### *8.1.2.2 Causality Classification*

The relationship of an AE to IMP administration will be classified according to the following:

- **Related:** reports including good reasons and sufficient information (for example plausible time sequence, dose response relationship, pharmacology, positive dechallenge and/or rechallenge) to assume a causal relationship with IMP administration in the sense that it is plausible, conceivable or likely.
- **Not related:** reports including good reasons and sufficient information (for example implausible time sequence and/or attributable to concurrent disease or other drugs) to rule out a causal relationship with IMP administration.

#### *8.1.2.3 Assessment of Expectedness*

The expectedness of an AE shall be determined by the sponsor according to the IB for an unapproved IMP, or the summary of product characteristics (SmPC) or package insert (PI) for an authorised medicinal product that is being used according to the terms and conditions of the marketing authorisation. If the IMP has marketing authorisations in several countries with different SmPCs or PIs, one will be selected as the reference document for assessing expectedness.

The reference document for assessing expectedness of AEs/event in this study will be the current (at time of study) triptorelin IB for triptorelin PR 3-month, and the PI (China) for triptorelin acetate PR 1-month.

#### *8.1.2.4 Laboratory Test Abnormalities*

Abnormalities in laboratory test values should only be reported as AEs if any of the following apply:

- They result in a change in IMP schedule of administration (change in dosage, delay in administration, IMP discontinuation),
- They require intervention or a diagnosis evaluation to assess the risk to the subject,
- They are considered as clinically significant by the investigator.

#### *8.1.2.5 Abnormal Physical Examination Findings*

Clinically significant changes, in the judgement of the investigator, in physical examination findings (abnormalities) will be recorded as AEs.

#### *8.1.2.6 Other Investigation Abnormal Findings*

Abnormal test findings as judged by the investigator as clinically significant (for example, ECG changes) that result in a change in IMP dosage or administration schedule, or in discontinuation of the IMP, or require intervention or diagnostic evaluation to assess the risk to the subject, should be recorded as AEs.

### *8.1.3 Recording and Follow Up of Adverse Events*

At each visit, the subject should be asked a nonleading question such as: “How have you felt since the last assessment?”

All observed or volunteered AEs, regardless of treatment group or suspected causal relationship to IMP, will be recorded on the AE page(s) of the eCRF. Events involving drug reactions, accidents, illnesses with onset during the treatment phase of the study, or exacerbations of pre-existing illnesses should be recorded, with the exception of endometriosis-related symptoms, which should only be recorded if they fulfil the criteria for an SAE (see Section 8.1.4).

Any AEs already recorded and designated as ‘continuing’ should be reviewed at each subsequent assessment.

For all AEs, the investigator must follow up and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to the sponsor or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE (i.e. IMP or other illness). The investigator is required to assess causality and record that assessment on the eCRF. Follow up of the AE, after the date of IMP discontinuation, is required if the AE or its sequelae persist. Follow up is required until the event or its sequelae resolve or stabilise at a level acceptable to the investigator and the sponsor’s clinical monitor or his/her designated representative.

### *8.1.4 Reporting of Serious Adverse Events*

All SAEs (as defined below) regardless of treatment group or suspected relationship to IMP must be reported immediately (within 24 hours of the investigator’s knowledge of the event) using the fax number specified at the beginning of this protocol. If the immediate report is

submitted by telephone, this must be followed by detailed written reports using the SAE report form.

An SAE is any AE that:

(1) Results in death,

(2) Is life threatening, that is any event that places the subject at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death,

(3) Results in in-patient hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons,

(4) Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions,

(5) Results in congenital anomaly/birth defect in the offspring of a subject who received the IMP,

(6) Is an important medical event that may not result in death, be life threatening, or require hospitalisation when, based upon appropriate medical judgement, may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalisation, or the development of drug dependency or drug abuse.

In addition to the above criteria, any additional AE that the sponsor or an investigator considers serious should be immediately reported to the sponsor and included in the corporate SAEs database system.

- Hospitalisation is defined as any in-patient admission (even if less than 24 hours). For chronic or long term in-patients, in-patient admission also includes transfer within the hospital to an acute/intensive care in-patient unit.
- **Prolongation of hospitalisation** is defined as any extension of an in-patient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, **as determined by the investigator or treating physician**. For protocol-specified hospitalisation in clinical studies, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment emergent, clinical AE (i.e. not associated with the development of a new AE or worsening of a pre-existing condition) may meet criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting to the sponsor.
- Preplanned or elective treatments/surgical procedures should be noted in the subject's screening documentation. Hospitalisation for a preplanned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequelae which meet the criteria for seriousness described above.

Any SAE must be reported immediately (within 24 hours) using the fax number specified at the beginning of this protocol, independent of the circumstances or suspected cause, if it occurs or comes to the attention of the investigator at any time during the study period.

Any AE/SAE with a suspected causal relationship to IMP administration occurring at any other time after completion of the study must be promptly reported.

The following information is the minimum that must be provided to the sponsor within 24 hours for each SAE:

- Study number
- Centre number
- Subject number
- AE
- Investigator's name and contact details

The additional information included in the SAE form must be provided to the sponsor or representative as soon as it is available. The investigator should always provide an assessment of causality for each event reported to the sponsor. Upon receipt of the initial report, the sponsor will ask for the investigator's causality assessment if it was not provided with the initial report.

The investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications.

### *8.1.5 Pregnancy*

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP has interfered with a contraceptive method. If pregnancy occurs during the study, the outcome of the pregnancy will then need to be collected poststudy and it may be necessary to discontinue administration of the IMP.

Information regarding pregnancies must be collected on the AE page of the eCRF and reported to the sponsor as an SAE. The sponsor will request further information from the investigator as to the course and outcome of the pregnancy using the Standard Pregnancy Outcome Report Form.

The investigator must instruct all female subjects to inform them immediately should they become pregnant during the study. The investigator should counsel the subject, discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the subject should continue until conclusion of the pregnancy, which may involve follow up after the subject’s involvement in the study has ended.

Pregnancies with a conception date within 150 days (for subjects receiving triptorelin pamoate PR 3-month), or 90 days (for subjects receiving triptorelin acetate PR 1-month) after subject’s last dose of the study drug must also be reported to the investigator for onward reporting to the sponsor.

### *8.1.6 Deaths*

All AEs resulting in death during the study period, must be reported as an SAE within 24 hours of the investigator’s knowledge of the event.

The convention for recording death is as follows:

- AE term: lead cause of death
- Outcome: fatal.

The **only exception** is if the cause of death is unknown (i.e. sudden or unexplained death), in which case the AE term may be “death” or “sudden death”.

### *8.1.7 Discontinuation/Withdrawal due to Adverse Events/Serious Adverse Events*

Discontinuation/withdrawal due to AEs should be distinguished from discontinuation/withdrawal due to insufficient response to the IMP (see Section 4.3).

If the IMP is discontinued due to an SAE, it must be reported immediately, as described in Section 8.1.4.

In all cases, the investigator must ensure the subject receives appropriate medical follow up (see Section 8.1.3).

### *8.1.8 Reporting to Competent Authorities/IECs/IRBs/Other Investigators*

The sponsor will ensure that processes are in place for submission of reports all SAEs occurring during the study to the CA, IECs and other investigators concerned by the IMP. Reporting will be in accordance with the applicable regulatory requirements.

## 8.2 Clinical Laboratory Tests

Blood and urine samples will be collected at screening (Visit 1), Week 12 (Visit 5) and Week 24 (Visit 8) for the evaluation of haematology, blood biochemistry and urinalysis.

The investigator will review the safety laboratory test results, document the review, and record any clinically relevant changes occurring or observed during the study in the AE section of the eCRF (see Section 8.1.2.4 for abnormal laboratory tests that should be recorded as AEs).

All clinically relevant abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return to baseline or to a level deemed acceptable by the investigator and the sponsor's clinical monitor (or his/her designated representative) or until the abnormality is explained by an appropriate diagnosis.

### *8.2.1 Haematology*

Blood samples (2 mL) will be collected in a potassium ethylenediaminetetraacetic acid (EDTA) tube to assess the following parameters: red blood cell (RBC) count, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and platelet count.

### *8.2.2 Blood Biochemistry*

Blood samples (2.5 mL) will be collected in an activator gel tube to assess the following parameters:

- urea, creatinine, total bilirubin, conjugated bilirubin;
- chloride, bicarbonate, sodium, potassium, calcium, inorganic phosphate;
- alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase;
- albumin, total protein, total cholesterol, triglycerides, fasting glucose.

### *8.2.3 Urinalysis*

Fresh urine samples (at least 10 mL) will be collected to assess the following parameters: pH, protein, ketones, glucose, bilirubin, blood, urobilinogen and specific gravity by dipstick.

### *8.2.4 Pregnancy Test*

A human chorionic gonadotrophin (HCG) urine test will be performed for subjects at screening (Visit 1) and baseline (Visit 2, Day 1) and analysed locally. Any subject becoming pregnant during the study will be withdrawn. All pregnancies that occur during the study are to be reported as described in Section 8.1.5.

### *8.2.5 Hormones*

Measurements of serum $E_2$, FSH and LH concentrations will be performed at a central laboratory at Week 40, only if a subject's menses has not recovered by this timepoint. Hormone measurements at other timepoints are considered efficacy assessments, and are described, along with methods for the assessment of $E_2$, FSH and LH concentrations, in Section 7.3.1.

## 8.3 Physical/Pelvic Examination

Physical examinations, including pelvic examination, will be conducted at screening (Visit 1), Week 12 (Visit 5) and Week 24 (Visit 8). Subject height and weight will be measured at screening only.

Any clinically significant physical examination findings (abnormalities) observed during the study will be reported as AEs. Any physical examination findings (abnormalities) persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

## 8.4 Pelvic Type B Ultrasound Scan

A pelvic type B ultrasound investigation will be performed at screening (Visit 1; a result within 1 month prior to screening will be acceptable) and at Week 24 (Visit 8). An additional (optional) scan may be conducted at Week 12 (Visit 5) based on the subject's condition, as judged by the investigator.

Any clinically significant pelvic type B ultrasound findings (abnormalities) observed during the study will be reported as AEs.

## 8.5 Vital Signs

Blood pressure and heart rate will be recorded at screening (Visit 1), baseline (Visit 2, Day 1) Weeks 4, 8, 12, 16, 20, 24 (Visits 3 to 8), and at the end of study/early withdrawal visit.

Blood pressure and heart rate will be recorded after five minutes rest in a sitting position.

## 8.6 Electrocardiography

An ECG analysis will be included as a safety evaluation/endpoint in this study.

The computerised 12-lead ECGs will be recorded at screening (Visit 1), Week 12 (Visit 5) and Week 24 (Visit 8).

Specific machine details will be provided in the Study Manual. Sinus rhythm, heart rate, PR interval, QRS interval, QT interval/corrected QT interval (QTc) will be recorded, as well as clinical significance. A paper copy of each ECG trace will be printed; these copies must be signed by the investigator and identified with subject screening number, initials, date of assessment and study visit. The ECG will be recorded with the subject in supine position after five minutes of rest until four regular consecutive complexes are available.

All ECGs will be evaluated by qualified persons at the study site, and any clinically significant abnormalities observed during the study will be recorded as AEs.

# 9 ASSESSMENTS OF PHARMACOKINETICS/PHARMACODYNAMICS

Sparse PK samples will be taken in all subjects (in addition to the full PK/PD subgroup) at Day 1 (baseline) and Weeks 4, 8, 12 and 24 (see Table 2). A full triptorelin PK analysis will be performed in a subgroup of up to 16 subjects in each treatment group (the full PK/PD subgroup; to be enrolled at selected sites). Full PK samples will be collected in accordance with Table 3 and Table 4 for subjects in this subgroup. Additional hormone samples ($E_2$, FSH and LH) will also be collected at Weeks 1, 2, 3 and 32 in this subgroup.

## 9.1 Pharmacokinetics

### *9.1.1 Sample Collection*

Blood samples for the assay of triptorelin will be collected in Vacutainer tubes at the timepoints indicated in Table 2, Table 3 and Table 4. Full details of sample collection, processing, required labelling, storage and the shipment process for these samples will be documented in the Study Manual.

On predetermined dates, samples will be shipped to the central laboratory under frozen conditions. For security reasons, aliquots of each sample will be shipped separately. The batch containing the second aliquot will not be shipped until the first one has arrived.

Upon receipt at the central laboratory, samples will be checked and stored until analysis.

Surplus plasma samples may be shipped outside China for the purposes of cross-validating the bioanalytical method used in this study. Surplus plasma samples will be managed anonymously, and will not be identifiable.

### *9.1.2 Analytical Procedures*

The concentration of triptorelin will be analysed using a validated specific and sensitive method, and in accordance with GLP. All details of sample collection, handling, shipment, methodology and reference ranges will be provided in the Study Manual and archived in the TMF.

### *9.1.3 Data Analysis*

Details of the statistical and analytical methods to be applied to the PK data are provided in Section 10.4.4.

## 9.2 Pharmacodynamics

Additional PD assessments will be conducted on the full PK/PD subgroup, comprising up to 32 subjects enrolled at selected sites.

Additional blood samples will be collected at Week 1, Week 2, Week 3 and Week 32 (in accordance with Table 3) for the analysis of $E_2$, FSH and LH, as described in Section 7.3.1.

## 9.3 Pharmacokinetics/Pharmacodynamics Relationship

A PK/PD analysis (PK/PD modelling) will be performed for triptorelin pamoate PR 3-month and triptorelin acetate PR 1-month exploring the relationship between plasma triptorelin concentrations and serum $E_2$, FSH and LH, where possible.

Additional population PK/PD modelling may be conducted. This analysis will be described in a separate data analysis plan and reported in a standalone report.

# 10 STATISTICS

## 10.1 Analyses Sets

The following analysis sets will be used during statistical analyses:

- **Screened set:** All subjects screened (i.e. who signed the informed consent).
- **Randomised set:** All subjects randomised (i.e. who were randomly allocated to a treatment group).
- **Safety set:** All subjects who received at least one dose of study medication.
- **Full analysis set (FAS):** All randomised subjects who received at least one dose of study medication with at least one baseline and at least one post-baseline assessment of the primary efficacy parameter.
- **Per protocol (PP) set:** All subjects in the FAS for whom no major protocol violations/deviations occurred.
- **Full PK profile analysis set** (for noncompartmental analysis (NCA)): Subjects in the full PK/PD subgroup who have received at least one dose of IMP and have no major protocol deviations affecting the PK variables, and who have a sufficient number of PK concentration measurements to estimate the main PK parameters (maximum observed plasma concentration ($C_{max}$) and time to maximum observed plasma concentration ($t_{max}$), plus area under the plasma concentration-time curve for the dosing interval ($AUC_{\tau}$) for subjects receiving triptorelin pamoate PR 3-month).
- **Sparse PK sampling analysis set:** All subjects who received at least one dose of IMP and have no major protocol deviations affecting the PK variables and who have at least one valid plasma concentration.
- **PD analysis set:** All subjects in the full PK/PD subgroup who have a sufficient number of PD measurements.
- **PK/PD relationships set:** All subjects who receive at least one dose of IMP and have at least one valid plasma triptorelin concentration and at least one PD measurement.

### *10.1.1 Data Sets Analysed*

Analysis of the primary and secondary efficacy endpoints will be performed on the FAS and the PP set. All exploratory efficacy analyses will be performed on the FAS. PK analyses will be performed on the full PK profile analysis set and the sparse PK sampling analysis set, as appropriate.

The analyses of safety data will be performed based on the safety set.

### *10.1.2 Subject Allocation and Reasons for Exclusion from the Analyses*

Any major protocol deviation types will be described in the Protocol Deviation Document (PDD) and their impact on inclusion in each analysis set for any subject will be specified. The final list of protocol deviations impacting each analysis set will be reviewed during the blind data review meeting held prior to database lock, without reference to treatment group assignment for individual subjects.

## 10.2 Sample Size Determination

Sample size was estimated based on data from Ipsen Study E-28-52014-705.[5] Assuming the percentage of subjects castrated at Week 12 of triptorelin acetate PR 1-month treatment is no less than 92%, a sample size of 133 subjects in each treatment group will have 85% power to

demonstrate the noninferiority of triptorelin pamoate PR 3-month to the comparator, when the lower limit of the 95% confidence interval (CI) of the difference in percentage of subjects castrated at Week 12 between the treatment groups is >-10% and with a 0.025 one-sided type I error rate.

Assuming that the dropout rate will be around 10%, a sample size of 300 randomised subjects in total is planned for this study.

## 10.3 Significance Testing and Estimations

A two sided 95% CI for the difference of the two castration rates (triptorelin pamoate PR 3-month treatment group minus triptorelin acetate PR 1-month treatment group) will be calculated. If and only if the lower limit of the 95% CI is greater than the lower limit of equivalence region (-10%), triptorelin pamoate PR 3-month treatment will be confirmed to be noninferior to triptorelin acetate PR 1-month treatment.

## 10.4 Statistical/Analytical Methods

Statistical analyses will be performed by an external CRO, managed by the sponsor's Biometry Department.

A statistical analysis plan (SAP) describing the planned statistical analysis in detail with tables, figures and listings (TFLs) templates will be developed as a separate document and will be approved prior to enrolment of the first subject into the study.

Statistical evaluation will be performed using Statistical Analysis System (SAS®) (version 9).

### *10.4.1 Demographic and Other Baseline Characteristics*

In order to assess the balance of treatment groups, descriptive summary statistics (number of available observations (n), mean, standard deviation (SD), median, minimum, maximum) or frequency counts of demographic (age, age category, ethnicity, race) and baseline data (endometriosis history, significant medical/surgical history, concomitant disease (predosing AEs and ongoing medical history), prior medications and therapies including those for endometriosis) will be presented by treatment group and overall for the randomised, safety (if different from randomised) and PP sets and the FAS.

### *10.4.2 Homogeneity of Treatment Groups*

In order to assess the homogeneity of treatment groups at baseline, treatment groups will be compared descriptively for demographic and baseline characteristics (see Section 10.4.1).

### *10.4.3 Subject Disposition and Withdrawals*

The numbers and percentages of subjects enrolled and included in each of the PP set, FAS and safety set will be tabulated overall, by treatment group and by centre. The reasons for subject exclusions from each of the analysis sets will also be tabulated. In addition, the numbers of subjects who were randomised, discontinued and completed will be tabulated by treatment group and overall. Primary reasons for discontinuation of study treatment will be tabulated.

### *10.4.4 Pharmacokinetic Data*

Individual plasma concentrations of triptorelin for triptorelin pamoate PR 3-month and triptorelin acetate PR 1-month will be listed and summarised by timepoint using descriptive statistics for continuous variables (n, mean, median, SD, minimum, maximum, geometric mean, and geometric coefficient of variation (assuming log normally distributed data)). Linear and semilogarithmic plots of individual and mean plasma concentration time profiles, as well as spaghetti plots will be reported separately for subjects in the triptorelin pamoate PR 3-month full PK/PD subgroup.

The PK analysis of triptorelin concentrations will be performed using an NCA approach using the Phoenix WinNonlin PK program version 6.3 or higher. The following PK parameters will be calculated for the triptorelin pamoate PR 3-month:

- Minimum observed plasma concentration during the dosing interval ($C_{min}$) after the first dose and at steady state
- $C_{max}$ after the first and last administration (steady state)
- $t_{max}$ after the first and last administration (steady state)
- $AUC_{\tau}$ after first and last administration (steady state) estimated by the log linear trapezoidal rule

The following PK parameters will be calculated for the triptorelin acetate PR 1-month group:

- $C_{max}$ and $t_{max}$ after the first dose
- $C_{min}$ after the first, and each subsequent administration (steady state)

Additional PK parameters may be calculated, if appropriate.

Descriptive statistics of PK parameters will be presented for the full PK profile analysis set. PK parameters will be summarised by n, median, minimum, maximum, geometric mean, and geometric coefficient of variation except for $t_{max}$ where only n, median, minimum and maximum values will be reported.

In addition to the NCA described above, analyses will be performed in all subjects (population PK modelling), to assess the PK profile of triptorelin pamoate PR 3-month and triptorelin acetate PR 1-month in all subjects. These analyses will be described in a separate data analysis plan and reported in a standalone report.

### *10.4.5 Pharmacodynamic Data*

A PK/PD analysis (PK/PD modelling) will be performed for triptorelin pamoate PR 3-month and triptorelin acetate PR 1-month exploring the relationship between plasma triptorelin concentrations and serum $E_2$, FSH and LH, where possible.

Additional population PK/PD may be conducted. This analysis will be described in a separate data analysis plan and reported in a standalone report.

### *10.4.6 Efficacy Evaluation*

#### *10.4.6.1 Primary Efficacy Endpoint*

The primary efficacy variable is the percentage of subjects castrated ($E_2 \leq 184$ pmol/L or 50 pg/mL) at Week 12.

The number and percentage of subjects castrated ($E_2 \leq 184$ pmol/L or 50 pg/mL) at Week 12 will be summarised by treatment group and the difference, including 2-sided 95% CI for the difference between treatment groups will be presented. If the lower limit of the 95% CI for the difference in percentage of subjects castrated ($E_2 \leq 184$ pmol/L or 50 pg/mL) at Week 12 between the triptorelin pamoate PR 3-month and triptorelin acetate PR 1-month is >-10%, noninferiority of triptorelin pamoate PR 3-month will be confirmed.

#### *10.4.6.2 Secondary Efficacy Endpoints*

***Percentage of Subjects Castrated ($E_2 \leq 184$ pmol/L or 50 pg/mL) at Weeks 4 and 8 and Percentage of Subjects Castrated ($E_2 \leq 110$ pmol/L or 30 pg/mL) at Weeks 4, 8 and 12:***

The number and percentage of subjects castrated (according to each criterion) will be presented by treatment group for each visit. The difference between the treatment groups will be calculated and displayed with the 95% CI for the true treatment difference.

***Change in Endometriosis-Associated Pelvic Pain (by 10 cm VAS) at Weeks 4, 8 and 12:***

Endometriosis-associated pelvic pain measured by 10 cm VAS and change from baseline, will be summarised overall and for the subgroup of subjects with baseline VAS>3 cm at each time point, using summary statistics (n, mean, median, SD and minimum and maximum values) and the 95% CI for the true difference in mean VAS score and VAS change from baseline scores will be presented.

***Serum $E_2$, FSH and LH Concentration at Weeks 4, 8 and 12:***

Serum $E_2$, FSH and LH concentrations and change from baseline will be summarised at each time point, using descriptive statistics (n, mean, median, SD and minimum and maximum values) and the 95% CI for the difference between treatment groups in mean concentration values and mean change from baseline values will be presented for each parameter.

***Time to Menses Recovery:***

Time to menses recovery will be defined as the time (in days) between date of last dose of study drug and date of first day the subject observed menstrual bleeding of the next menstrual period. Any subjects withdrawing from the study without menstrual bleeding will be censored in the analysis at the date of withdrawal, and any subjects without menstrual bleeding prior to the end of study visit will be censored in this analysis at the date of the end of study visit.

The distribution of times to menses recovery will be estimated using the Kaplan-Meier method for each treatment group and presented graphically and median time to event and 95% CIs will be provided for each treatment group.

*10.4.6.3* Exploratory Efficacy Endpoints

***Percentage of Subjects Castrated 1) $E_2 \leq 184$ pmol/L or 50 pg/mL 2) $E_2 \leq 110$ pmol/L or 30 pg/mL at Week 24:***

The number and percentage of subjects castrated at Week 24 (according to each criterion) will be presented by treatment group. The difference between the treatment groups will be calculated and displayed with the 95% CI for the true treatment difference.

***Change in Endometriosis-associated Pelvic Pain (by 10 cm VAS) at Weeks 16, 20 and 24 and the End of Study Visit Compared to Baseline:***

Endometriosis-associated pelvic pain measured by 10 cm VAS and change from baseline, will be summarised overall and for the subgroup of subjects with baseline VAS>3 cm at each time point, using summary statistics (n, mean, median, SD and minimum and maximum values) and the 95% CI for the true difference in mean VAS score and VAS change from baseline scores will be presented.

***Serum $E_2$, FSH and LH Concentration at Week 24:***

Serum $E_2$, FSH and LH concentrations at Week 24 and change from baseline will be presented using summary statistics (n, mean, median, SD and minimum and maximum values) and the 95% CI for the difference between treatment groups in mean concentration values and mean change from baseline values will be presented for each parameter.

### *10.4.7 Adjustment for Centre Effect*

Centre effect will be considered in analysis of the primary endpoint.

### *10.4.8 Safety Evaluation*

All safety data will be included in the subject data listings. Analyses and summary tables will be based upon the safety set.

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version current at the start of the study, and will be classified by MedDRA preferred term and system organ class. AE listings will be presented by subject, system organ class and preferred term.

The incidence of all reported treatment-emergent adverse events (TEAEs) and SAEs will be tabulated by treatment group and overall. In addition, summary tables will be presented by maximum intensity, drug relationship and TEAEs associated with premature withdrawal of study medication.

A TEAE is defined as any AE that occurs from receiving the first dose of study drug to the end of study/early withdrawal visit if:

- it was not present prior to receiving the first dose of study drug, or
- it was present prior to receiving the first dose of study drug but the intensity increased during the active phase of the study.

All TEAEs will be flagged in the AE listings.

Prior and concomitant medication will be coded by using the World Health Organisation (WHO) Drug Dictionary (version December 2016 or above) and will be summarised separately by treatment group and overall with the number and percentage of subjects receiving prior and concomitant medication by drug class and preferred drug name. Prior medications/therapies are all those stopped prior to the first dose of study drug and concomitant medications/therapies are defined as all those ongoing or started at/after the first dose of study drug.

For laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented. Shift tables will be presented of the number and percentage of subjects with low, normal or high values and normal or abnormal physical/pelvic examination findings between baseline and Week 24 time points.

Vital signs data will be presented as shift tables, with the number and percentage of subjects with normal or abnormal findings between baseline and each assessment.

ECG data will also be presented as shift tables, with the number and percentage of subjects with normal or abnormal findings between baseline and Week 12 and Week 24.

Serum $E_2$, FSH and LH concentrations at Week 40 will be listed only.

Detailed methodology for the analysis of safety data will be presented in the SAP.

### 10.5 Subgroup Analyses

Endometriosis-associated pelvic pain and change from baseline will also be assessed at each timepoint for the subgroup of subjects with VAS>3 cm at baseline.

### 10.6 Interim Analyses

No interim analyses will be performed.

# 11 DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

Authorised personnel from external CAs and sponsor authorised Quality Assurance personnel may carry out inspections and audits. The purpose of an audit is to ensure that ethical, regulatory and quality requirements are fulfilled in all studies performed by the sponsor.

Auditors and inspectors must have direct access to study documents and site facilities as specified in Section 12.4, and to any other locations used for the purpose of the study in question (for example laboratories).

In the event of the site being notified directly of a regulatory inspection, the investigator must notify the sponsor's representative as soon as possible, to assist with preparations for the inspection.

# 12 QUALITY CONTROL AND QUALITY ASSURANCE

## 12.1 Protocol Amendments and Protocol Deviations and Violations

### *12.1.1 Protocol Amendments*

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favourable opinion of a written amendment by the IEC/IRB, except when necessary to eliminate immediate safety concerns to the subjects or when the change involves only logistics or administration. The principal investigator and the sponsor will sign the protocol amendment.

### *12.1.2 Protocol Deviations, Violations, and Exceptions*

A protocol deviation is nonadherence to protocol-specific study procedures or schedules that does not involve inclusion/exclusion criteria, primary objective evaluation criteria, and/or GCP guidelines. Deviations are considered minor and do not impact the study.

A protocol violation is any significant divergence from the protocol, i.e. nonadherence on the part of the subject, the investigator, or the sponsor to protocol specific inclusion/exclusion criteria, primary objective evaluation criteria, and/or GCP guidelines. Protocol violations will be identified and recorded, by study centre personnel, on the eCRF.

As a matter of policy, the sponsor will not grant exceptions to protocol-specific entry criteria to allow subjects to enter a study. If under extraordinary circumstances such action is considered ethically, medically, and scientifically justified for a particular subject, prior approval from the sponsor and the responsible IEC/IRB, in accordance with the Standard Operating Procedure (SOP), is required before the subject will be allowed to enter the study. If investigative centre personnel learn that a subject who did not meet protocol eligibility criteria was entered in a study (a protocol violation), they must immediately inform the sponsor. Such subjects will be discontinued from the study, except in an exceptional instance following review and written approval by the sponsor and the responsible IEC/IRB, according to the applicable SOP.

## 12.2 Information to Study Personnel

The investigator is responsible for giving information about the study to all staff members involved in the study or in any element of subject management, both before starting any study procedures and during the course of the study (for example, when new staff become involved). The investigator must assure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities. These study staff members must be listed on the study centre authorisation form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study staff, including the investigator, and for ensuring their compliance with the protocol. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

## 12.3 Study Monitoring

The investigator is responsible for the validity of all data collected at the site.

The sponsor is responsible for monitoring this data to verify that the rights and wellbeing of subjects are protected, that study data are accurate (complete and verifiable to source data) and that the study is conducted in compliance with the protocol, GCP and regulatory requirements.

Sponsor-assigned monitors will conduct regular site visits. The investigator will allow direct access to all relevant files (for all subjects) and clinical study supplies (dispensing and storage areas) for the purpose of verifying entries made in the eCRF, and assist with the monitor's activities, if requested. Adequate time and space for monitoring visits should be made available by the investigator.

The site must complete the eCRFs according to the sponsor monitoring manual, of the subject's visit and on an ongoing basis to allow regular review by the study monitor, both remotely by the internet and during site visits. The central study monitor at the sponsor will use functions of the electronic data capture (EDC) system to address any queries raised while reviewing the data entered by the study site personnel in a timely manner.

Whenever a subject name is revealed on a document required by the sponsor (for example, laboratory print outs) the name must be blacked out permanently by the site personnel, leaving the initials visible, and annotated with the subject number as identification.

### 12.4 Audit and Inspection

Authorised personnel from external CAs and the sponsor's authorised Quality Assurance personnel may carry out inspections and audits (see Section 11).

### 12.5 Data Quality Assurance

Monitored eCRFs transferred from the investigational site to the assigned Data Management group will be reviewed (secondary monitoring) for completeness, consistency, legibility and protocol compliance.

Reasons should be given on the relevant eCRF for any missing data and other protocol deviations. Any electronic queries and items not adequately explained will require additional electronic manual queries to be raised to the investigator by the monitor for clarification/correction. The investigator must ensure that queries are dealt with promptly. All data changes and clarifications can be viewed in the audit trail function of the eCRF.

# 13 ETHICS

## 13.1 Compliance with Good Clinical Practice and Ethical Considerations

This study will be conducted in compliance with IECs/IRBs, informed consent regulations, the Declaration of Helsinki and ICH GCP Guidelines (Section 1.6). In addition, this study will adhere to all local regulatory requirements.

Before initiating a study, the investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB for the study protocol/amendment(s), written informed consent form, any consent form updates, subject emergency study contact cards, subject recruitment procedures (for example, advertisements), any written information to be provided to subjects and a statement from the IEC/IRB that they comply with GCP requirements. The IEC/IRB approval must identify the protocol version, as well as the documents reviewed.

After IEC/IRB approval, changes will require a formal amendment. Once the study has started, amendments should be made only in exceptional circumstances. Changes that do not affect subject safety or data integrity are classified as administrative changes and generally do not require ethical approval. If ethically relevant aspects are concerned, the IEC/IRB must be informed and, if necessary, approval sought prior to implementation. Ethical approval on administrative changes will be obtained if required by local/site IEC/IRB.

## 13.2 Informed Consent

Prior to study entry, the investigator, or a person designated by the investigator, will explain the nature, purpose, benefits and risks of participation in the study to each subject, subject's legally acceptable representative or impartial witness. Written informed consent must be obtained prior to the subject entering the study (before initiation of any study-related procedure and administration of the IMP). Sufficient time will be allowed to discuss any questions raised by the subject.

The sponsor will provide a sample informed consent form. The final version-controlled form must be agreed to by the sponsor, and the IEC/IRB and must contain all elements included in the sample form, in language readily understood by the subject. Each subject's original consent form, personally signed and dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion, will be retained by the investigator. The investigator will supply subjects with a copy of their signed informed consent.

The consent form may need to be revised during the study should important new information become available that may be relevant to the safety of the subject or as a result of protocol amendments. In this instance approval should always be given by the IEC/IRB. It is the investigator's responsibility to ensure that all subjects subsequently entered into the study and those currently in the study sign the amended form. This is documented in the same way as previously described. Subjects who have completed the study should be informed of any new information that may impact on their welfare/wellbeing.

The investigator should, with the consent of the subject, inform the subject's primary physician about their participation in the clinical study.

### 13.3 Health Authorities and Independent Ethics Committees/Institutional Review Boards

As required by local regulations, the sponsor's Regulatory Affairs group will ensure all legal regulatory aspects are covered, and obtain approval of the appropriate regulatory bodies, prior to study initiation in regions where an approval is required.

### 13.4 Confidentiality Regarding Study Subjects

The investigator must assure that the privacy of the subjects, including their personal identity and all personal medical information, will be maintained at all times. In eCRFs and other documents or image material submitted to the sponsor, subjects will be identified not by their names, but by an identification code (for example, initials and identification number).

Personal medical information may be reviewed for the purpose of verifying data recorded on the eCRF. This review may be conducted by the study monitor, properly authorised persons on behalf of the sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

# 14 DATA HANDLING AND RECORD KEEPING

## 14.1 Data Recording of Study Data

In compliance with GCP, the medical records/medical notes, etc, should be clearly marked and permit easy identification of a subject's participation in the specified clinical study.

The investigator must record all data relating to protocol procedures, IMP administration, laboratory data, safety data and efficacy ratings on the eCRFs provided for the study. The investigator, by completing the signature log, may formally designate authority to complete eCRFs to appropriately qualified staff having certified user access to the eCRF. Subject completed diaries and questionnaires will be printed or electronic.

The investigator must, as a minimum, provide an electronic signature (e-signature) to each eCRF to attest to the accuracy and completeness of all the data. If any changes are made to the eCRF, after a form has been locked and electronically signed, the investigator will be required to perform an additional e-signature authorising agreement with any new information or changes to the eCRF.

All corrections on the eCRF will be automatically tracked and a reason for change is always required. In the eCRF, the audit trail function will allow the changes made to be viewed on each item entered.

## 14.2 Data Management

EDC will be utilised for collecting subject data. Each site is required to have a computer and internet connection available for site entry of clinical data. All entries in the eCRF will be done under the electronic signature of the person performing the action. This electronic signature consists of an individual and confidential username and password combination. It is declared to be the legally binding equivalent of the handwritten signature. Only sponsor-authorised users will have access to the eCRF as appropriate to their study responsibilities. Users must have successfully undergone software application training prior to entering data into the eCRF.

Data management will be conducted either by a CRO, directed by the sponsor's data management department or by the sponsor's data management department. All data management procedures will be completed in accordance with the sponsor and the contracted CRO SOPs. Prior to data being received in-house at the assigned CRO, it will be monitored at the investigator site, (for further details please see Section 12.3 Study Monitoring). The eCRF and other data documentation removed from the investigator site(s) will be tracked by the CRO and the monitor.

The sponsor will ensure that an appropriate eCRF is developed to capture the data accurately, and suitable queries are raised to resolve any missing or inconsistent data. The investigator will receive their data, from the clinical study, in an electronic format (PDF files) which will be an exact copy of the eCRF, and will include the full audit trail, for archiving purposes and future reference.

Any queries generated during the data management process will also be tracked by the contracted data management CRO/will be raised within the EDC system. It is the central study monitor's responsibility to ensure that all queries are resolved by the relevant parties.

The sponsor will also ensure that SAE data collected in the eCRF are consistent with information provided to the sponsor's pharmacovigilance department (and vice versa).

The coding of an AE, medical history and concomitant medication terms will be performed by the contracted CRO/a CRO, directed by the sponsor's Biometry Group, and reviewed and

approved by the sponsor. Concomitant medications will be coded using the WHO drug dictionary and AEs/medical history terms will be coded using MedDRA (see Section 10.4.8).

## 14.3 Record Archiving and Retention

During the prestudy and initiation visits, the monitor must ensure the archiving facilities are adequate and archiving/retention responsibilities of the investigator have been discussed.

Study documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 15 years) or at least 2 years have elapsed since the formal discontinuation of clinical development of the product. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. The investigator should take measures to prevent accidental or premature destruction of these documents. The final archiving arrangements will be confirmed by the monitor when closing out the site. The sponsor will inform the investigator, in writing, as to when these documents no longer need to be retained.

If the principal investigator relocates or retires, or otherwise withdraws his/her responsibility for maintenance and retention of study documents, the sponsor must be notified (preferably in writing) so that adequate provision can be made for their future maintenance and retention.

# 15 FINANCING AND INSURANCE

## 15.1 Contractual and Financial Details

The investigator (and/or, as appropriate, the hospital administrative representative) and the sponsor will sign a clinical study agreement prior to the start of the study, outlining overall sponsor and investigator responsibilities in relation to the study. Financial remuneration will cover the cost per included subject, based on the calculated costs of performing the study assessments in accordance with the protocol, and the specified terms of payment will be described in the contract. The contract should describe whether costs for pharmacy, laboratory and other protocol required services are being paid directly or indirectly.

## 15.2 Insurance, Indemnity and Compensation

The sponsor will provide Product Liability insurance for all subjects included in the clinical study. Where required, a hospital specific indemnity agreement will be used.

# 16 REPORTING AND PUBLICATIONS OF RESULTS

## 16.1 Publication Policy

The sponsor encourages acknowledgement of all individuals/organisations involved in the funding or conduct of the study, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the sponsor.

The results of this study may be published or communicated to scientific meetings by the investigators involved in the study. For multicentre studies, a plan for scientific publication and presentation of the results may be agreed and implemented by the study investigators or a Steering Committee. The sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or paper before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. The sponsor will undertake to comment on the draft documents within the time period agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the sponsor and authors (or the author's institution). Requested amendments will be incorporated by the author, provided they do not alter the scientific value of the material.

If patentability would be adversely affected by publication, this will be delayed until (i) a patent application is filed for the content of the publication in accordance with applicable provisions of the clinical trial agreement concerned, (ii) the sponsor consents to the publication, or (iii) the time period as may be agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the sponsor and authors (or authors' institution) after receipt of the proposed publication by the sponsor, whichever of (i), (ii) or (iii) occurs first.

The author undertakes to reasonably consider the sponsor's request for delay to the proposed publication should the sponsor reasonably deem premature to publish the results obtained at the then stage of the study.

## 16.2 Clinical Study Report

A final clinical study report (CSR) will be prepared according to the ICH guideline on structure and content of CSRs. A final CSR will be prepared where any subject has signed informed consent, regardless of whether the study is completed or prematurely terminated. Where appropriate an abbreviated report may be prepared. The CSR will be in compliance with any applicable regulatory requirements, national laws in force and will be in English and Chinese.

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## 18 LIST OF APPENDICES

# Appendix 1 Visual Analogue Scale

## Visual Analogue Scale:

Please indicate the subjective level of your most severe endometriosis pain over the last 4 weeks*.
Mark it with a single vertical mark on the line.


Patients record the severity of their pain on a VAS score from 0 mm to 100 mm.

* For the Day 1 (baseline) assessment, subjects who have undergone endometriotic surgery within 4 weeks prior to the assessment must assess their most severe level of endometriosis-associated pain post-surgery