AN OPEN-LABEL, MULTICENTRE, SINGLE-ARM STUDY TO ASSESS THE EFFICACY AND SAFETY OF TRIPTORELIN 3-MONTH FORMULATION IN CHINESE CHILDREN WITH CENTRAL PRECOCIOUS PUBERTY

STUDY PROTOCOL
STUDY NUMBER: D-CN-52014-243

Triptorelin Pamoate 15 mg for injection (3-month formulation)

Version 1.0: 27 July 2020
Version 2.0 including Global Amendment 1: 28 October 2020
Version 3.0 including Global Amendment 2: 16 March 2021
Version 4.0 including Global Amendment 3: 09 July 2021

Study Sponsor:
Ipsen Pharma
65, Quai Georges Gorse
92100 Boulogne Billancourt, France
Tel: PPD

Study Phase: III

Sponsor Signatory:
PPD
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For serious adverse event (SAE) and for pregnancy reporting:
E-mail: CCI
If email reporting is not possible:
Fax: PPD

INVESTIGATOR'S AGREEMENT

Investigator Agreement and Signature:

I have read and agree to the protocol titled "An Open-Label, Multicentre, Single-Arm Study to Assess the Efficacy and Safety of Triptorelin 3-Month Formulation in Chinese Children with Central Precocious Puberty" (D-CN-52014-243) with Amendment #3. I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP), Good Pharmacovigilance Practices (GVP), 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:

DATE:

OFFICE:

Sponsor's Representative Signature:

NAME:

TITLE: SIGNATURE:

DATE:

OFFICE:

COORDINATING INVESTIGATOR'S AGREEMENT

Coordinating Investigator Agreement and Signature:

I have read and agree to the protocol titled "An Open-Label, Multicentre, Single-Arm Study to Assess the Efficacy and Safety of Triptorelin 3-Month Formulation in Chinese Children with Central Precocious Puberty" (D-CN-52014-243) with Amendment #3. I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP), Good Pharmacovigilance Practices (GVP), 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: PPD

TITLE: COORDINATING INVESTIGATOR

SIGNATURE: PPD

DATE: PPD

OFFICE: PPD

SYNOPSIS

Name of Sponsor/company: Ipsen Pharma

Name of finished product: Triptorelin pamoate 15 mg for injection

Name of active ingredient(s): Triptorelin pamoate (henceforth referred to as triptorelin)

Title of study: An open-label, multicentre, single-arm study to assess the efficacy and safety of triptorelin 3-month formulation in Chinese children with central precocious puberty

Study number: D-CN-52014-243

Number of planned centres: The study will be conducted in approximately 5 to 10 sites in China

Planned study period:	**Phase of development**:
Q1 2021 to Q1 2022 ***Extension:*** Q3 2021 to Q3 2022	Phase III

Study type: A prospective, open-label, multicentre, single-arm, interventional study

Objectives of the Main study:

Primary Objective:

The primary objective of the study is to assess the efficacy of the triptorelin 3-month prolonged release (PR) formulation in suppressing luteinising hormone (LH) levels to pre-pubertal levels (defined as a peak LH ≤3 IU/L after intravenous (i.v.) gonadotropin-releasing hormone (GnRH) stimulation) at Month 3 in Chinese children with central precocious puberty (CPP).

Secondary Objectives:

- To assess the efficacy in suppressed LH response to GnRH test at Month 6
- To assess follicle-stimulating hormone (FSH) response to GnRH test at Month 3 and Month 6
- To assess LH and FSH levels at Month 3 and Month 6
- To assess sex hormone serum concentrations (oestradiol for girls and testosterone for boys) at Month 3 and Month 6
- To assess sexual maturation (pubertal stage as per Tanner method) at Month 6
- To assess auxological parameters including height, growth velocity, weight and body mass index (BMI) at Month 3 and Month 6
- To assess bone age (BA), the difference between BA and chronological age (CA) at Month 6
- To assess gonadal development as determined by uterine length in girls and testicular volume in boys at Month 6
- To assess the safety profile.

Exploratory Objective:

- To assess plasma triptorelin levels at Day 1, Month 3 and Month 6.

Objectives of the Extension Phase

To describe the long-term efficacy and safety of Triptorelin 3-month prolonged release formulation through following objectives:

- To assess the percentage of subjects with suppressed LH hormones at Month 12
- To assess LH and FSH levels at Month 9 and 12
- To assess sex hormone serum concentrations (oestradiol for girls and testosterone for boys) at Month 9 and 12
- To assess sexual maturation (pubertal stage as per Tanner method) at Month 12
- To assess auxological parameters including height, growth velocity, weight and body mass index (BMI) at Month 9 and Month 12
- To assess bone age (BA), the difference between BA and chronological age (CA) at Month 12
- To assess gonadal development as determined by uterine length in girls and testicular volume in boys at Month 12
- To assess the safety profile.

Study Hypothesis: The effectiveness of triptorelin 3-month formulation in Chinese population of CPP children has the same or similar trend with that in overseas CPP population.

Methodology:

The study is a prospective, open-label, multicentre, single-arm, interventional study intended to evaluate the efficacy and safety of triptorelin 3-month formulation in Chinese children with CPP.

Main study phase:

Participants will be treated with an intramuscular (i.m.) injection of triptorelin on Day 1 of the study and at Month 3 (3 months after the first injection). Triptorelin injections do not have to be adapted based on body weight but the participant should have a minimum weight of 20 kg.

The study consists of a Screening period (up to 28 days before enrolment), during which participants with CPP will be screened for eligibility before receiving the first triptorelin injection (Day 1 of the study). They will visit the study centre at Month 3 and Month 6 for efficacy and safety assessments. Participants will receive a total of two injections during the study period before they attend the End of Study (EOS) visit at Month 6.

Each participant is expected to be enrolled in this study for a minimum of 6 months and up to 7 months (including Screening period).

Participants who complete the study will perform final procedures and assessments at the final visit (Month 6). Participants who withdraw from the study before the completion of the evaluation period will be invited to attend an Early Withdrawal visit to perform early discontinuation procedures and assessments.

Extension phase:

The extension of the study will provide the possibility for subjects to continue with their study drug treatment, per investigators decision, for an additional 6 months. This will imply a triptorelin injection at Month 6 and an additional triptorelin injection at Month 9, before

they attend the End of Extension Phase (EOEP) visit at Month 12. This Extension phase is optional.

Each participant may be treated with the study drug for up to 12 months.

Number of participants planned:

Approximately 32 participants, including three boys, will be enrolled in the study.

Diagnosis and criteria for inclusion:

Main study phase:

Inclusion criteria:

Participants must fulfil all the following criteria to be included in the study:

(1) Provision of written informed consent prior to any study-related procedures. Consent should be provided by the parent(s)/legal guardian. If determined by local requirements, a signed assent must be obtained from the paediatric participant

(2) Evidence of CPP documented by:

- Onset of development of secondary sex characteristics (breast development in girls or testicular enlargement in boys according to the Tanner method: Stage II) before the age of 8 years in girls and 9 years in boys
- Pubertal response of LH to GnRH stimulation test (stimulated peak LH ≥5 IU/L) in both sexes
- Difference between BA and CA >1 year
- Girls with Tanner staging ≥2 for breast development and who have enlarged uterine length and several follicles with diameter >4 mm in the ovary observed by pelvic type B ultrasound at the Screening visit; boys who have testicular volume ≥4 mL observed by testicular type B ultrasound at the Screening visit

(3) Age less than 9 years old for girls and less than 10 years old for boys at initiation of triptorelin treatment

(4) Weight at least 20 kg

(5) Girls who have already had menophania/menarche must have a negative pregnancy test prior to the start of study treatment and should not be at risk of pregnancy throughout the study period.

Exclusion criteria:

Participants will be ineligible for study participation if they meet any of the following criteria:

(1) Gonadotropin-independent (peripheral) precocious puberty: extrapituitary secretion of gonadotropins or gonadotropin-independent gonadal or adrenal sex steroid secretion

(2) Non-progressing isolated premature thelarche

(3) Presence of an unstable intracranial tumour or an intracranial tumour requiring neurosurgery or cerebral irradiation. Participants with hamartomas not requiring surgery are eligible

(4) Evidence of renal (creatinine >1.5 x upper limit of normal (ULN)) or hepatic impairment (bilirubin >1.5 x ULN or alanine aminotransferase (ALT)/aspartate transaminase (AST) >3 x ULN)

(5) Any other condition or chronic illness or treatment possibly interfering with growth or other study endpoints (e.g. chronic steroid use except topical steroids, renal failure, diabetes, moderate to severe scoliosis)

(6) Prior or current therapy with a GnRH agonist (GnRHa), medroxyprogesterone acetate, growth hormone or insulin-like growth factor-1 (IGF-1)

(7) Diagnosis of short stature, i.e. >2.25 standard deviation (SD) below the mean height for age

(8) Major medical or psychiatric illness that could interfere with study visits

(9) Known hypersensitivity to any of the test materials or related compounds

(10) Use of anticoagulants (heparin and coumarin derivatives) within the 2 weeks prior to the Screening visit.

Extension phase:

(11) Subjects will qualify for the extension phase if they sign the corresponding specific consent form, are still benefiting from treatment at the end the primary study and have not experienced any unacceptable safety issues.

Test product, dose, mode of administration:

The test product is triptorelin pamoate 15 mg for injection (manufactured by Ipsen Pharma Biotech), which was created to guarantee the release of 11.25 mg of triptorelin. It is presented as a slightly yellow freeze-dried cake or powder in a glass vial. The solvent provided for injection is a 2 mL ampoule of mannitol and water for injection.

The triptorelin 3-month formulation is to be administered by i.m. route only. The powder is reconstituted with the solvent for suspension and should be injected immediately after preparation.

Duration of treatment:

Main study phase:

6 months (i.e. two injections)

Extension phase:

An additional 6 months will be given (i.e. two injections)

Reference therapy, dose and mode of administration:

Not applicable.

Criteria for evaluation (endpoints):

Main study phase:

Efficacy:

Primary Endpoint and Evaluation:

The primary endpoint in this study is the proportion of children with LH suppression defined as stimulated peak LH ≤3 IU/L after GnRH stimulation at Month 3. The GnRH stimulation test is performed by using an i.v. injection of gonadorelin (synthetic GnRH) to stimulate gonadotrophin release and blood samples will be collected prior to and 30, 60 and 90 minutes (±5 minutes at each timepoint) after the gonadorelin injection for central assessment of serum LH levels.

Secondary Endpoints and Evaluations:

- Change in basal serum LH and FSH levels at Month 3 and Month 6 compared to baseline

- Proportion of children with LH suppression defined as stimulated peak LH ≤3 IU/L after GnRH stimulation at Month 6
- Change in peak LH level after the GnRH stimulation test at Month 3 and Month 6 compared to baseline
- Change in peak FSH level after the GnRH stimulation test at Month 3 and Month 6 compared to baseline
- Proportion of children with pre-pubertal levels of sex steroids (defined as oestradiol ≤20 pg/mL in girls and testosterone ≤0.3 ng/mL in boys) at Month 3 and Month 6
- Change in oestradiol levels in girls and testosterone levels in boys at Month 3 and Month 6 compared to baseline
- Change in pubertal stage using the Tanner method (genital stage in boys, breast stage in girls and pubic hair stage in both sexes) at Month 6 compared to baseline
- Proportion of children with stabilised pubertal stage compared to baseline stage using the Tanner method at Month 6
- Change in auxological parameters including height, growth velocity, weight and BMI at Month 3 and Month 6 compared to baseline
- Change in BA, difference between BA and CA at Month 6 compared to baseline
- Change in uterine length in girls and testicular volume in boys at Month 6 compared to baseline.

Safety:

- Incidence of treatment-emergent adverse events (TEAEs) throughout the study, including local tolerability
- Change in clinical safety laboratory (blood biochemistry, haematology and urinalysis) parameters at Month 3 and 6
- Change in physical examination and vital signs (blood pressure and heart rate) measurements at each visit.

Pharmacokinetics:

Exploratory Endpoint:

- To assess sparse plasma triptorelin concentrations at Day 1, Month 3 and Month 6.

Extension phase:

For subjects participating into the extension study following endpoints will be analysed:

Efficacy:

- Proportion of children with LH suppression (defined as LH ≤3 IU/L) at Month 12
- Change in basal serum LH and FSH levels at Month 9 and Month 12
- Proportion of children with pre-pubertal levels of sex steroids (defined as oestradiol ≤20 pg/mL in girls and testosterone ≤0.3 ng/mL in boys) at Month 9 and Month 12
- Change in oestradiol levels in girls and testosterone levels in boys at Month 9 and Month 12
- Change in pubertal stage using the Tanner method (genital stage in boys, breast stage in girls and pubic hair stage in both sexes) at Month 12
- Proportion of children with stabilised pubertal stage compared to baseline stage using the Tanner method at Month 12
- Change in auxological parameters including height, growth velocity, weight and BMI at Month 9 and Month 12

- Change in BA, difference between BA and CA at Month 12
- Change in uterine length in girls and testicular volume in boys at Month 12

Safety:

- Incidence of treatment-emergent adverse events (TEAEs) throughout the study, including local tolerability
- Change in clinical safety laboratory (blood biochemistry, haematology and urinalysis) parameters at Months 9 and 12
- Change in physical examination and vital signs (blood pressure and heart rate) measurements at each visit.

Statistical Methods:

Main study phase:

The analysis sets for the primary and secondary efficacy endpoints will be the Intention-To-Treat set (ITT), the modified Intention-To-Treat set (mITT) and the per protocol (PP) set.

Due to the small sample size and potential wider precision of the estimator, the primary endpoint will be summarised descriptively. No formal hypothesis test will be performed.

For the primary efficacy endpoint, the summary statistics of number and percentage of participants and the exact two-sided 90% confidence interval (CI) for a binomial proportion will be computed by Statistical Analysis System (SAS®) using the exact binomial distributions on the mITT (primary analysis), ITT and PP.

For secondary efficacy endpoints related to a change at Month 6 compared to baseline, the descriptive summary statistics (number of participants (n), mean, SD, median, minimum, maximum) will be calculated on the mITT. In addition, secondary efficacy endpoints may be performed on the PP. Exact two-sided 90% CIs will also be constructed for all secondary endpoints expressed as proportions.

All safety data will be included in the participant data listings. Analyses and summary tables will be based upon the Safety population.

Sample size calculation: The purpose of this study is to observe whether the effectiveness in Chinese population of CPP children has the same or similar trend with that in overseas CPP population, mainly using descriptive statistical analysis. Although no formal statistical testing will be carried out, the following assumptions were made, based on global pivotal study 2-54-52014-143 [Zenaty 2016], for the sample size to enable an evaluation of the trend of effectiveness:

- Expected outcome for the proportion of children with a suppressed LH response to the GnRH test (stimulated peak LH ≤3 IU/L) at Month 3 is 90%
- Null proportion is 70%
- An exact binomial test of a proportion with a one-sided nominal significance level of 0.05 and power =85%
- Expected common dropout rate =10%.

Under these assumptions, approximately 32 (28 with additional 10% dropouts) participants, including at least three boys, are planned to be enrolled into the study in order

to observe the efficacy of the triptorelin 3-month formulation in the proportion of children with a suppressed LH response to the GnRH stimulation test at Month 3.

Extension phase:

A separate analysis on efficacy and safety endpoints will be performed considering the extension phase duration, a period of an additional 6 months, lasting until the End of Extension Phase visit at Month 12.

As this is an extension phase following the main study phase, the efficacy and safety endpoints in the extension phase will be summarised descriptively. No formal statistical hypotheses testing will be performed.

Statistical analyses will include the following:

- For the continuous endpoints, the descriptive summary statistics (number of participants (n), mean, SD, median, minimum, maximum) will be calculated
- For the categorical endpoints, the summary statistics of number and percentage of participants and the exact two-sided 90% confidence interval (CI) will be calculated

The analysis sets for the efficacy endpoints will be the Intention-To-Treat set (ITT) and the per protocol (PP) set. Analyses and summary tables for the safety endpoints will be based upon the Safety population.

Sample size calculation: The number of participants included in the extension study will be dependent on the number of participants from study D-CN-52014-243 who give consent to continue into the extension study. A maximum of 32 participants will be expected to be enrolled in the extension phase.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	09 July 2021 (Version 4.0)
Amendment 2	16 March 2021 (Version 3.0)
Amendment 1	28 October 2020 (Version 2.0)
Original Protocol	27 July 2020 (Version 1.0)

The details of the previous amendments are provided in Appendix 2.

Amendment 3 (09 July 2021, Version 4.0)

Overall Rationale for the Amendment:

This amendment includes minor updates and clarifications of study assessments, as well as alignment of common text with latest protocol template update.

Summary of change table from previous version of the protocol

Any new or amended text in the protocol is indicated in bold. Deletions are marked in strikeout text. Minor formatting and editing are not included.

Section	WAS (Version 3.0, 16 March 2021)	IS (Version 4.0, 09 July 2021)	Rationale
Title Page		**Study Phase: III**	Quality assurance requirement to follow latest protocol template update.
Title Page	~~Emergency Contact:~~ PPD ~~Ipsen Innovation ZI de Courtaboeuf 5 avenue du Canada 91940 Les Ulis, France Mobile:~~ PPD		Aligned with current template
Synopsis (Criteria for evaluation (endpoints, Primary Endpoint and Evaluation))	The GnRH stimulation test is performed by using an i.v. injection of gonadorelin (synthetic GnRH) to stimulate gonadotrophin release and blood samples will be collected prior to and 30, 60 and 90 minutes after the gonadorelin injection for central assessment of serum LH levels.	The GnRH stimulation test is performed by using an i.v. injection of gonadorelin (synthetic GnRH) to stimulate gonadotrophin release and blood samples will be collected prior to and 30, 60 and 90 minutes **(±5 minutes at each timepoint)** after the gonadorelin injection for central assessment of serum LH levels.	More feasible to have a time window for blood collection.

Section	WAS (Version 3.0, 16 March 2021)	IS (Version 4.0, 09 July 2021)	Rationale
4.5 / Temporary Discontinuation		**4.5 Temporary Discontinuation** **In case of suspected or confirmed COVID-19 (SARS-CoV-2) infection, the intervention administration may be temporarily discontinued depending on the participant's clinical presentation. In some cases, the investigator may request a participant be retested before the intervention administration is resumed.**	Section added to align with recent protocol template update.
4.6 / Lost to Follow-up		**4.6 Lost to Follow-up** **A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.** **The following actions must be taken if a participant fails to return to the clinic for a required study visit:** • **The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The site should counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.** • **Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, three telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.** • **Should the participant continue to be**	

Section	WAS (Version 3.0, 16 March 2021)	IS (Version 4.0, 09 July 2021)	Rationale
		unreachable, he/she will be considered to have withdrawn from the study.	
4.7 / Screen Failures		**A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes date of informed consent, demography, reason for screen failure, eligibility criteria and any SAE.**	
5.1 / Study Schedule	Table 1: Footnote (f): GnRH test samples for LH and FSH concentrations will be collected at 30, 60 and 90 minutes after the GnRH test. The LH and FSH samples will all be taken before injection of triptorelin, if applicable (e.g. Month 3 visit). Table 2: Footnote (b): GnRH test samples for LH and FSH concentrations will be collected at 30, 60 and 90 minutes after the GnRH test. The LH and FSH samples will all be taken before injection of triptorelin, if applicable ~~**(e.g. Month 3 visit)**~~.	Table 1: Footnote (f): GnRH test samples for LH and FSH concentrations will be collected at 30, 60 and 90 minutes (**±5 minutes at each timepoint**) after the GnRH test. The LH and FSH samples will all be taken before injection of triptorelin, if applicable (e.g. Month 3 visit). Table 2: Footnote (b): GnRH test samples for LH and FSH concentrations will be collected at 30, 60 and 90 minutes (**± 5 minutes at each timepoint**) after the GnRH test. The LH and FSH samples will all be taken before injection of triptorelin, if applicable.	More feasible to have a time window for blood collection.

Section	WAS (Version 3.0, 16 March 2021)	IS (Version 4.0, 09 July 2021)	Rationale
6.3 / Concomitant Medication/Therapy	The following concomitant medications are not permitted during this study: • Any treatment or procedure with ~~an~~ effect on the metabolism or secretion of gonadotropins (LH or FSH) or sex steroids (oestradiol and/or testosterone) will be considered as a protocol violation; • All drugs mentioned as prohibited in the exclusion criteria remain prohibited during the study period: GnRH analogues (other than triptorelin 3-month formulation), medroxyprogesterone acetate, growth hormone or IGF-1, systemic or inhaled steroids (mild topical steroids are permitted), anticoagulants (heparin and coumarine derivatives).	The following concomitant medications/**procedures** are not permitted during this study: • Any treatment or procedure with **a definitive or potential effect** on the metabolism or secretion of gonadotropins (LH or FSH) or sex steroids (oestradiol and/or testosterone) will be considered as a protocol violation; • All drugs mentioned as prohibited in the exclusion criteria remain prohibited during the study period: GnRH analogues (other than triptorelin 3-month formulation), medroxyprogesterone acetate, growth hormone or IGF-1, systemic or inhaled steroids (mild topical steroids are permitted), anticoagulants (heparin and coumarine derivatives). • **Any concurrent investigational agent or procedure.**	Investigational agents, other than those planned for this study, may impact efficacy and safety data and should not be allowed during study participation.

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6.5 / Procedures for Monitoring Participant Compliance	The Investigator will be responsible for monitoring participant compliance. Participants may be withdrawn from the study at any time if the Investigator or the Sponsor determines that the participant is not in compliance with the study protocol (see Section 4.4 for details).	The Investigator will be responsible for monitoring participant compliance. Participants may be withdrawn from the study at any time if the Investigator or the Sponsor determines that the participant is not in compliance with the study protocol (see Section 4.4 for details). **When participants are dosed at the site, they will receive triptorelin directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the site will be recorded in the source documents and in the CRF. The dose of triptorelin and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the injection.**	Section added to align with recent protocol template update.
7.4.2 / Gonadotropin-releasing Hormone Stimulation Test	Blood samples will be collected prior to gonadorelin injection (timepoint T0) and at 30 minutes (T30), 60 minutes (T60) and 90 minutes (T90) after a single i.v. injection of gonadorelin with 2.5 µg/kg (maximum 100 µg).	Blood samples will be collected prior to gonadorelin injection (timepoint T0) and at 30 minutes (T30), 60 minutes (T60) and 90 minutes (T90) (**±5 minutes at each timepoint**) after a single i.v. injection of gonadorelin with 2.5 µg/kg (maximum 100 µg).	More feasible to have a time window for blood collection
7.4.5 / Auxological Parameters, Bone Age and Chronological Age Measurements and Gonad Development	~~Target height and percentile height for age will be obtained from Tanner tables [Tanner 1965].~~ Bone age determination (in years and months) will be performed by X-rays of the hand and wrist and estimated by the Greulich and Pyle method [Greulich 1959].	Bone age determination (in years and months) will be performed by X-rays of the hand and wrist and estimated by the Greulich and Pyle method [Greulich 1959].	Correction of a misinterpretation of the data that should be collected.
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 (e.g.~~	**These** definitions include events occurring from the time the participant gives informed consent until the end of the study (as defined in Section 3.8). **AE Definition:** • **An AE is any untoward medical occurrence in a clinical study participant,**	Text aligned with recent protocol template update.

Section	WAS (Version 3.0, 16 March 2021)	IS (Version 4.0, 09 July 2021)	Rationale
	~~nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings). In clinical studies an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no triptorelin has been administered.~~ ~~This~~ definition includes events occurring from the time the participant gives informed consent until the end of the study (as defined in Section 3.8).	**temporally associated with the use of study intervention, whether or not considered related to the study intervention.** **NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.** **Events Meeting the AE Definition:** • **Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e. not related to progression of underlying disease).** • **Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.** • **New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.** • **Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.** • **Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an**	

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		intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Event NOT Meeting the AE Definition: • Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).	

Section	WAS (Version 3.0, 16 March 2021)	IS (Version 4.0, 09 July 2021)	Rationale
		• **Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.**	
8.1.5 / Reporting of Serious Adverse Events	An SAE is ~~any AE that~~: (1) Results in death (2) Is life threatening, ~~that is any event that places the participant 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 (see below)~~ (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~~ … ~~In addition to the above criteria, any treatment-related non-serious AE or 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~~.	An SAE is **defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed**: (1) Results in death (2) Is life threatening. **The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.** (3) **Requires** in-patient hospitalisation or prolongation of existing hospitalisation. **In general, hospitalisation signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered**	Text aligned with recent protocol template update.

Section	WAS (Version 3.0, 16 March 2021)	IS (Version 4.0, 09 July 2021)	Rationale
		serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. (4) Results in a persistent or significant disability/incapacity. **The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza and accidental trauma (e.g sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.**	
11.4.4.1 / Primary Efficacy Endpoint	The GnRH stimulation test is performed by using i.v. injection of gonadorelin (synthetic GnRH) to stimulate gonadotrophin release, and blood samples will be collected prior to and 30, 60, 90 minutes after the gonadorelin injection for central assessment of serum LH levels.	The GnRH stimulation test is performed by using i.v. injection of gonadorelin (synthetic GnRH) to stimulate gonadotrophin release, and blood samples will be collected prior to and 30, 60, 90 minutes **(±5 minutes at each timepoint)** after the gonadorelin injection for central assessment of serum LH levels.	More feasible to have a time window for blood collection
14.2 / Informed Consent for Participation in the Study	~~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 participant, participant's legally acceptable representative or impartial witness. Written informed~~	• **The informed consent form and any participant/assent recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws. They must**	

Section	WAS (Version 3.0, 16 March 2021)	IS (Version 4.0, 09 July 2021)	Rationale
	~~consent must be obtained prior to the participant entering the study (before initiation of any study related procedure and administration of triptorelin). Sufficient time will be allowed to discuss any questions raised by the participant.~~ ~~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 participant. Each participant's original consent form, personally signed and dated by the participant or by the participant's legally acceptable representative and by the person who conducted the informed consent discussion, will be retained by the Investigator. The Investigator will supply participants with a copy of their signed informed consent form.~~ ~~The informed 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 participant 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 participants subsequently entered into the study and those currently in the study sign the amended form. This is documented in the same way as described above. Participants who have completed the study should be informed of any new information that may impact their welfare/wellbeing.~~ ~~The Investigator should, with the consent of the participant, inform the participant's primary physician about their participation in the clinical study.~~	be approved prior to use as described in Section 14.1. • The investigator or his/her authorised representative will explain to the participant and their legally authorised representative the nature and objectives of the study and possible risks and benefits associated with the participation. They will answer all questions regarding the study. • Participants and their legally authorised representative must be informed that their participation is voluntary. • The investigator or his/her authorised representative will obtain written informed consent/assent from each participant and the legally authorised representative before any study-specific procedure is performed. The investigator will retain the original of each participant's signed informed consent/assent form. • A copy of the signed informed consent must be provided to the participant and their legally authorised representative. • The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the informed consent form. • Participants must be re-consented to the most	

Section	WAS (Version 3.0, 16 March 2021)	IS (Version 4.0, 09 July 2021)	Rationale
		current version of the informed consent form during their participation in the study. If changes to the informed consent do not apply to all participants, this will be communicated to the IRB/IEC with a rationale. IRB/IEC approval must be received before implementation as required by local regulations. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study.	

Other documents impacted

Informed consent form	Yes ☐	No ☒
Case report form (CRF)	Yes ☒	No ☐
Statistical analysis plan (SAP)	Yes ☐	No ☒

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LIST OF ABBREVIATIONS

ABBREVIATION	Wording Definition
AE(s)	Adverse Event(s)
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Transaminase
BA	Bone Age
BMI	Body Mass Index
CA	Chronological Age
CBC	Complete Blood Count
CE	Conformité Européenne
CRF	Code of Federal Regulations (US)
CI	Confidence Interval
CPP	Central Precocious Puberty
CRO	Contract Research Organisation
CSR	Clinical Study Report
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GnRH	Gonadotropin-releasing Hormone
GnRHa(s)	GnRH Agonist(s)
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IGF-1	Insulin-like Growth Factor 1
i.m.	Intramuscular
INN	International Non-proprietary Name
IRB	Institutional Review Board
ITT	Intention-to-treat

ABBREVIATION	Wording Definition
IU	International Units
i.v.	Intravenous
IWRS	Interactive Web Response System
LH	Luteinising hormone
LHRH	Luteinising Hormone-releasing Hormone
MAH	Marketing Authorisation Holder
MDSS	Material Data Safety Sheets
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention-to-treat
N	Number of Participants
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
PASS	Power Analysis and Sample Size
PIL	Patient Information Leaflet
PK	Pharmacokinetic
PP	Per Protocol
PR	Prolonged Release
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System®
SD(s)	Standard Deviation(s)
SMP	Safety Management Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR(s)	Suspected Unexpected Serious Adverse Reaction(s)
t½	Plasma Half-life
TEAE(s)	Treatment-emergent Adverse Event(s)
ULN	Upper Limit of Normal
WHO-DD	World Health Organization Drug Dictionary

1 BACKGROUND INFORMATION

1.1 Introduction

Precocious puberty is a condition that causes early sexual development in girls and boys. While the chronological age (CA) limit for the onset of puberty is 8 years in girls and 9 years in boys for children in North America and Western European countries [Carel 2008], children with precocious puberty exhibit precocious pubertal development that can be 2.5 to 3 standard deviations (SDs) earlier than the current estimated average. The prevalence of precocious puberty is 10 times higher in girls than in boys [Carel 2008].

In a minority of children, precocious puberty can occur due to an organic lesion (cerebral tumour); in most children, this condition is caused by the early release of gonadotropin-releasing hormone (GnRH, also known as luteinising hormone-releasing hormone; LHRH) by the hypothalamus. In healthy children, GnRH stimulates the release of pituitary gonadotropins follicle-stimulating hormone (FSH) and luteinising hormone (LH), which is then followed by prolonged suppression of these hormones, contributing to normal pubertal development. The form of precocious puberty caused by early GnRH stimulation is termed central precocious puberty (CPP). In children with CPP, early GnRH release leads to the precocious secretion of LH and FSH which, in turn, activate the early secretion of gonadal hormones by the ovaries or testes.

Signs of puberty include pubic and axillary hair grow and changes in the child's body shape and behaviour. Boys develop facial hair and their penis lengthens and girls develop breasts and may have menstrual periods. In children with CPP, these signs prematurely appear before the age of 8 and 9 in girls and boys, respectively. Furthermore, growth velocity accelerates, initially inducing a rapid height increase, which stops at an early age. Accelerated bone maturation leads to premature epiphyseal closure and a final height below the target height that was otherwise expected for the child's age. These premature changes may also lead to psychological disorders in children with CPP.

There is currently no nationwide epidemiology study of CPP data in China. Only two studies have been published about the incidence of precocious puberty in two cities: Jiu Jiang (study with 3,312 children investigated and an incidence of 0.68%, 1.25% in girls and 0.11% in boys) [Hu 2012] and Zhengzhou (study with 8,750 children investigated and an incidence of 0.74%, 1.37% in girls and 0.26% in boys) [Wei 2010]. In coastal areas of China, precocious puberty has an incidence rate of 0.38%; the incidence in girls is higher at 0.67%. The prevalence of precocious puberty in Shanghai is 100/10,000 [Lin 2004]. These data refer to precocious puberty without GnRH-dependent stimulation, which is not specific for CPP and are probably lower than numbers described above.

As reported by Carel and Léger [Carel 2008], the assessment of gonadotropin levels (based on ultrasensitive assays) is central to the diagnosis of CPP. The gold standard for evaluation is the measurement of gonadotropin levels after stimulation with GnRH or a GnRH agonist (GnRHa). Peak LH levels of 5 to 8 IU/L suggest progressive CPP but there is an overlap between prepubertal and early pubertal values [Carel 2008, Resende 2007]. Caution should be taken when interpreting gonadotropin levels in children younger than 2 to 3 years old as gonadotropin levels are normally high in this age group [Carel 2008].

In CPP (i.e. with no other identified cause such as a cerebral tumour), there is no surgical therapy available and no effective alternative therapeutic option other than taking a prolonged release (PR) formulation of synthetic GnRH. In severe cases, untreated CPP causes physical and psychological problems for the child.

Treatment with GnRH analogues, which act by downregulating pituitary GnRH receptors [Carel 2009, Comite 1981 Crowley 1981, Bertelloni 2013], represent the standard of care for

the treatment of CPP [Carel 2009]. Their efficacy to stop precocious development has been demonstrated and their use involves only minor adverse events (AEs). A review of CPP treatment by Krishna et al confirmed that treatment with PR formulations of GnRHas is safe, with relatively minor side effects, and supported that the outcome in terms of final height is favourable in most patients [Krishna 2019].

Diphereline® (international non-proprietary name (INN): triptorelin) is a synthetic GnRH analogue that is mainly characterised by the replacement of the L-glycine in the 6th position by a D-tryptophan. This structural modification increases both the resistance to enzymatic degradation and the affinity to the pituitary receptor, thus prolonging the plasma half-life ($t_{1/2}$) and increasing the potency of the drug.

In China, Diphereline® is available as a 1-month formulation, which is approved for use in patients with prostate cancer, CPP, endometriosis, fibromyomas and female infertility, and a 3-month formulation (containing 15 mg of triptorelin pamoate to ensure the release of 11.25 mg of product), which is approved for prostate cancer.

Several studies have assessed the efficacy and safety of triptorelin 3-month PR release formulation, including three Ipsen-sponsored phase III studies and two independent studies [Carel 2006, Martinez-Aguayo 2006, Zenaty 2016]. In 2017, Durand et al. [Durand 2017] performed a meta-analysis to assess the data available from a total of 153 children with CPP (13 boys and 140 girls) that had participated in the clinical studies and received treatment with this triptorelin formulation. Across all studies, the primary outcome was the proportion of children with suppressed LH response (peak LH ≤3 IU/L) to the GnRH test 3 months after triptorelin injection. Secondary outcomes included the proportion of children with suppressed peak LH response at 6 months, and the proportion of children with suppressed peak FSH response (≤3 IU/L), proportion of girls with suppressed oestradiol (≤20 pmol/L) and proportion of boys with suppressed testosterone (≤30 ng/dL) at 3 months [Durand 2017]. The authors concluded that the 3-month formulation of triptorelin was efficacious in suppressing LH peak and other gonadal hormones and in slowing the progression of CPP in children.

The worldwide marketing status of all triptorelin formulations of which Ipsen is the marketing authorisation holder (MAH) can be found in the Investigator's Brochure (IB). Further details/additional information regarding risks and benefits to participants may also be found in the IB.

A more detailed description of the product is provided in Section 3.7 and Section 6. Further details on administration procedures and dosage are provided in Section 6.2.

1.2 Population to Be Studied

This study will enrol Chinese participants with CPP less than 9 years old for girls and less than 10 years old for boys at initiation of triptorelin treatment.

1.3 Compliance Statement

The study will adhere to all local regulatory requirements and relevant company policies. The Sponsor will ensure that the countries where data are transferred to are able to provide an adequate level of data protection.

Before initiating the study, the Investigator/institution will obtain written and dated approval/favourable opinion from the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) for the study protocol/amendment(s), written informed consent form from the participants, any consent form updates, participant emergency study contact cards, participant recruitment procedures (e.g. advertisements), any written information to be provided to participants and a statement from the IEC/IRB that they comply with Good Clinical

Practice (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

Triptorelin pamoate 15 mg (3-month formulation) for injection is registered in China as Diphereline® 15 mg for the treatment of prostate cancer.

Currently, there have been no clinical studies with the 3-month formulation of triptorelin for CPP in China. For this reason, Ipsen is sponsoring this study, which is intended to provide data on the efficacy and safety of triptorelin pamoate 3-month formulation in Chinese children with CPP.

Henceforth in this protocol, triptorelin pamoate 15 mg will be referred to as 'triptorelin'.

2.2 Study Objectives

Main study objectives

The primary objective of the study is to assess the efficacy of the triptorelin 3-month PR formulation in suppressing LH levels to pre-pubertal levels (defined as a peak LH ≤3 IU/L) after intravenous (i.v.) GnRH stimulation at Month 3 in Chinese children with CPP.

The secondary objectives of the study are as follows:

- To assess the efficacy in suppressed LH response to GnRH test at Month 6
- To assess follicle-stimulating hormone (FSH) response to GnRH test at Month 3 and Month 6
- To assess LH and FSH levels at Month 3 and Month 6
- To assess sex hormone serum concentrations (oestradiol for girls and testosterone for boys) at Month 3 and Month 6
- To assess sexual maturation (pubertal stage as per Tanner method) at Month 6
- To assess auxological parameters including height, growth velocity, weight and body mass index (BMI) at Month 3 and Month 6
- To assess bone age (BA), the difference between BA and chronological age (CA) at Month 6
- To assess gonadal development as determined by uterine length in girls and testicular volume in boys at Month 6
- To assess the safety profile.

The pharmacokinetic (PK) exploratory objective is:

- To assess plasma triptorelin levels at Day 1, Month 3 and Month 6.

Objectives of the Extension Phase

To describe the long-term efficacy and safety of Triptorelin 3-month prolonged release formulation through following objectives:

- To assess the percentage of subjects with suppressed LH hormones at month 12
- To assess LH and FSH levels at Month 9 and 12
- To assess sex hormone serum concentrations (oestradiol for girls and testosterone for boys) at Month 9 and 12
- To assess sexual maturation (pubertal stage as per Tanner method) at Month 12
- To assess auxological parameters including height, growth velocity, weight and body mass index (BMI) at Month 9 and Month 12
- To assess bone age (BA), the difference between BA and chronological age (CA) at Month 12

- To assess gonadal development as determined by uterine length in girls and testicular volume in boys at Month 12
- To assess the safety profile.

2.3 Study Hypothesis

The study hypothesis is that the effectiveness of triptorelin 3-month formulation in Chinese population of CPP children has the same or similar trend with that in overseas CPP population.

3 STUDY DESIGN

3.1 General Design and Study Schema

The study is a prospective, open-label, multicentre, single-arm, interventional study intended to evaluate the efficacy and safety of triptorelin 3-month formulation in Chinese children with CPP.

Main study phase:

A total of 32 participants, including at least three boys, will be enrolled in the study and treated with an intramuscular (i.m.) injection of triptorelin on Day 1 of the study and at Month 3 (3 months after the first injection). Triptorelin injections do not have to be adapted based on body weight but the participant should have a minimum weight of 20 kg.

The study consists of a Screening period (the Screening visit will take place up to 28 days before enrolment), during which participants with CPP will be screened for eligibility before receiving the first triptorelin injection (Day 1 of the study) and will visit the study centre at Month 3 and Month 6 for efficacy and safety assessments (Figure 1). Participants will receive a total of two injections during the study period before they attend the End of Study (EOS) visit at Month 6.

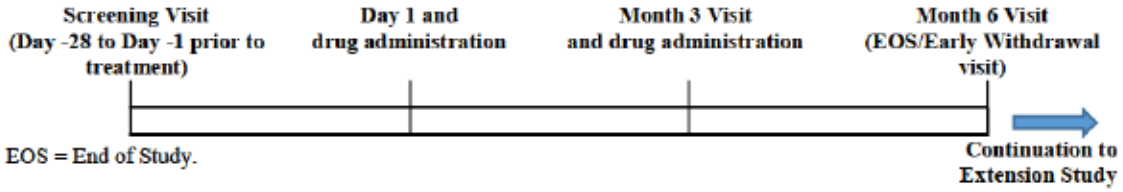
Each participant is expected to be enrolled in this study for a minimum of 6 months and up to 7 months (including Screening period).

Participants who complete the study will perform final procedures and assessments at the final visit (Month 6). Participants who withdraw from the study before the completion of the evaluation period will be invited to attend an Early Withdrawal visit to perform early discontinuation procedures and assessments.

Details for study procedures and schedule of assessments can be found in Section 5.

Specific details regarding study treatment are provided in Section 6.

Figure 1 Main Study Design

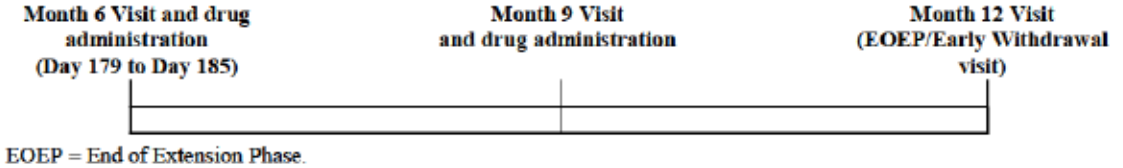


Extension phase:

The extension of the study will provide the possibility for subjects to continue with their study drug treatment, per investigators decision, for an additional 6 months. This will imply a triptorelin injection at the Month 6 Visit and an additional triptorelin injection at Month 9, before they attend the End of Extension Phase (EOEP) visit at Month 12. This Extension phase is optional.

Each participant may be treated with the study drug for up to 12 months.

Figure 2 Extension Phase Design



3.2 Primary and Secondary Endpoints and Evaluations

3.2.1 Primary Efficacy Endpoint and Evaluation

The primary endpoint is the proportion of children with LH suppression defined as stimulated peak LH ≤3 IU/L after GnRH stimulation at Month 3. The GnRH stimulation test is performed by using an i.v. injection of gonadorelin (synthetic GnRH) to stimulate gonadotrophin release and blood samples will be collected prior to and 30, 60 and 90 minutes after the gonadorelin injection for central assessment of serum LH levels.

3.2.2 Secondary Efficacy Endpoints and Evaluations

- Change in basal LH and FSH levels at Month 3 and Month 6 compared to baseline;
- Proportion of children with LH suppression defined as stimulated peak LH ≤3 IU/L after GnRH stimulation at Month 6
- Change in peak LH level after the GnRH stimulation test at Month 3 and Month 6 compared to baseline
- Change in peak FSH level after the GnRH stimulation test at Month 3 and Month 6 compared to baseline
- Proportion of children with pre-pubertal levels of sex steroids (defined as oestradiol ≤20 pg/mL in girls or testosterone ≤0.3 ng/mL in boys) at Month 3 and Month 6
- Change in oestradiol levels in girls or testosterone levels in boys at Month 3 and Month 6 compared to baseline
- Change in pubertal stage using the Tanner method (genital stage in boys, breast stage in girls and pubic hair stage in both sexes) at Month 6 compared to baseline
- Proportion of children with stabilised pubertal stage using the Tanner method at Month 6 compared to baseline
- Change in auxological parameters including height, growth velocity, weight, BMI at Month 3 and Month 6 compared to baseline
- Change in BA, difference between BA and CA at Month 6 compared to baseline
- Change in uterine length in girls or testicular volume in boys at Month 6 compared to baseline.

3.2.3 Safety Endpoints and Evaluations

Safety and tolerability will be assessed throughout the study by evaluating treatment-emergent adverse events (TEAEs), including local tolerability and injection site-related reactions), clinical laboratory test results, vital signs measurements, physical examination results and changes from baseline in concomitant medication usage. Safety parameters will be monitored at various timepoints from the time the participant provides informed consent to the end of the study, as follows:

- Incidence of TEAEs throughout the study, including local tolerability
- Change in clinical safety laboratory (blood biochemistry, haematology and urinalysis) parameters at Month 3 and 6
- Change in physical examination and vital signs (blood pressure and heart rate) measurements at each visit.

3.3 Extension Phase Efficacy and Safety Endpoints and Evaluations

3.3.1 Extension Phase Efficacy Endpoints and Evaluations

- Proportion of children with LH suppression (defined as LH ≤3 IU/L) at Month 12.

- Change in basal serum LH and FSH levels at Month 9 and Month 12
- Proportion of children with pre-pubertal levels of sex steroids (defined as oestradiol ≤20 pg/mL in girls and testosterone ≤0.3 ng/mL in boys) at Month 9 and Month 12
- Change in oestradiol levels in girls and testosterone levels in boys at Month 9 and Month 12
- Change in pubertal stage using the Tanner method (genital stage in boys, breast stage in girls and pubic hair stage in both sexes) at Month 12
- Proportion of children with stabilised pubertal stage compared to baseline stage using the Tanner method at Month 12
- Change in auxological parameters including height, growth velocity, weight and BMI at Month 9 and Month 12
- Change in BA, difference between BA and CA at Month 12
- Change in uterine length in girls and testicular volume in boys at Month 12

3.3.2 Extension Phase Safety Endpoints and Evaluations

- Incidence of treatment-emergent adverse events (TEAEs) throughout the study, including local tolerability
- Change in clinical safety laboratory (blood biochemistry, haematology and urinalysis) parameters at Months 9 and 12
- Change in physical examination and vital signs (blood pressure and heart rate) measurements at each visit.

3.4 Exploratory Pharmacokinetics Endpoint

- To assess sparse plasma triptorelin concentrations at Day 1, Month 3 and Month 6.

3.5 Randomisation and Blinding

This is a non-randomised, open-label study.

3.6 Maintenance of Randomisation and Blinding

Not applicable.

3.7 Study Treatments and Dosage

The investigational medicinal product is the triptorelin 3-month formulation, which will be administered by an i.m. injection on Day 1 and Month 3, for a total of two injections during the study. A more detailed description of administration procedures is given in Section 6.2.1.

Triptorelin is presented in a vial sealed with an halogenobutyl elastomer stopper and an aluminium crimp on which a polypropylene button is attached. The stoppered vial is clipped on a blister pack, which is then introduced in a carton box.

A complete carton box of the drug product contains:

- One type I clear glass 4 mL vial containing the sterile lyophilisate of microparticles with a halogenobutyl elastomer stopper and aluminium/polypropylene crimp
- One glass 2 mL ampoule of 2 mL sterile solvent
- One sterile blister pack

The vial and the ampoule are clipped on the back of the blister which is inserted in a preprinted paperboard carton box. The sterile heat formed blister pack has obtained the Conformité Européenne (CE) marking according to the medical device's regulation.

The blister pack contains:

- A hypodermic syringe

- Two hypodermic, single-use needles:
  - One used for transferring the suspension vehicle
  - One used for the i.m. injection.

The Sponsor's representative will receive a certificate of analysis for the batch of triptorelin to be used in the study, material data safety sheets (MDSS) for triptorelin and a packaging order that reflects the product release statement.

The core label texts for all packaging units will be written in Chinese and/or adjusted to be in compliance with applicable regulatory requirements (e.g. Good Manufacturing Practice (GMP) guidelines (Volume 4 Annex 13)), national laws in force and in accordance with the local languages. It will include:

- "Keep out of reach of children"
- "For clinical study use only"
- Name, address and telephone number of the Sponsor
- Storage conditions
- Expiry date
- Treatment number
- Batch number.

The Investigator or designee will only dispense triptorelin to study participants. The dispensing for each participant will be documented in the electronic case report form (eCRF).

At each triptorelin dispensation, a treatment number will be assigned by an Interactive Web Response System (IWRS). The IWRS will also manage all logistical aspects of the study treatment (e.g. replacement, drug supplies and expiry dates) and the recording of drug accountability/destruction. This service provides the Investigator, investigational site coordinators and project team members with a service that is available 24 hours a day, 7 days a week. Additional details may be found in the IWRS reference manual provided to each investigational site. In case of technical or dispensation queries, a 24-hour helpline is available (see supporting information in the Investigational Site File). If a participant discontinues the study before any intake of study treatment, his/her assigned treatment number(s) will not be reused.

In addition to the information provided in the IWRS, drug accountability paper records will be maintained by the Investigator.

3.8 Study Duration

This study includes a Screening period (up to 28 days prior to Day 1) and a 6 Month open-label dosing period with efficacy and safety assessments occurring at Month 3 and/or Month 6 visits, as indicated in Table 1. For this reason, the overall duration of the main study is planned to be a maximum of 7 months.

Each participant is expected to be enrolled in this study for a minimum of 6 months and up to 7 months (including Screening period) for the main study. Participation in the study will be considered to have ended at the time of the last visit (EOS visit).

The study will be considered to have started when the first participant has provided signed informed consent. The end of the main study will be when the last participant has completed the last follow-up visit in the study (Month 6).

Participants who complete the Month 6 study visit after confirmation of eligibility will be able to join an extension study to receive triptorelin for at least an additional 6 months, for a total

study duration of 12 months (13 months including Screening Period), or as judged clinically beneficial by the investigator.

The end of the extension study will be when the last participant has completed the last follow-up visit in the study (Month 12).

3.9 Source Data Recorded on the Case Report Form

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

The source documents must, as a minimum, contain a statement that the participant is included in a clinical study, the date that informed consent was obtained prior to participation in the study, the identity of the study, that diagnosis and eligibility criteria were met, visit dates, date and time of triptorelin administration and any AEs and associated concomitant medication.

As required by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)-E6, Section 6.4.9, if some items are recorded directly in the eCRF and are considered source data, the identification of these data must be documented and agreed upon 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 (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participants' 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, participant files and records kept at the pharmacy, at the laboratories and at medicotechnical departments involved in the clinical study).

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

4 SELECTION AND WITHDRAWAL OF PARTICIPANTS

4.1 Inclusion Criteria

Participants must fulfil all the following criteria to be included in the study:

(1) Provision of written informed consent prior to any study-related procedures. Consent should be provided by the parent(s)/legal guardian. If determined by local requirements, a signed assent must be obtained from the paediatric participant

(2) Evidence of CPP documented by:

- Onset of development of secondary sex characteristics (breast development in girls or testicular enlargement in boys according to the Tanner method: Stage II) before the age of 8 years in girls and 9 years in boys
- Pubertal response of LH to GnRH stimulation test (stimulated peak LH ≥5 IU/L) in both sexes
- Difference between BA and CA >1 year
- Girls with Tanner staging ≥2 for breast development and who have enlarged uterine length and several follicles with diameter >4 mm in the ovary observed by pelvic type B ultrasound at the Screening visit; boys who have testicular volume ≥4 mL observed by testicular type B ultrasound at the Screening visit

(3) Age less than 9 years old for girls and less than 10 years old for boys at initiation of triptorelin treatment

(4) Weight at least 20 kg

(5) Girls who have already had menophania/menarche must have a negative pregnancy test prior to the start of study treatment and should not be at risk of pregnancy throughout the study period.

4.2 Exclusion Criteria

Participants will be ineligible for study participation if they meet any of the following criteria:

(1) Gonadotropin-independent (peripheral) precocious puberty: extrapituitary secretion of gonadotropins or gonadotropin-independent gonadal or adrenal sex steroid secretion

(2) Non-progressing isolated premature thelarche

(3) Presence of an unstable intracranial tumour or an intracranial tumour requiring neurosurgery or cerebral irradiation. Participants with hamartomas not requiring surgery are eligible

(4) Evidence of renal (creatinine >1.5 x upper limit of normal (ULN)) or hepatic impairment (bilirubin >1.5 x ULN or alanine aminotransferase (ALT)/aspartate transaminase (AST) >3 x ULN)

(5) Any other condition or chronic illness or treatment possibly interfering with growth or other study endpoints (e.g. chronic steroid use except topical steroids, renal failure, diabetes, moderate to severe scoliosis)

(6) Prior or current therapy with a GnRH agonist (GnRHa), medroxyprogesterone acetate, growth hormone or insulin-like growth factor-1 (IGF-1)

(7) Diagnosis of short stature, i.e. >2.25 SD below the mean height for age

(8) Major medical or psychiatric illness that could interfere with study visits

(9) Known hypersensitivity to any of the test materials or related compounds

(10) Use of anticoagulants (heparin and coumarin derivatives) within the 2 weeks prior to the Screening visit.

4.3 Extension phase Inclusion Criteria

(11) Subjects will qualify for the extension phase if they sign the corresponding specific consent form, are still benefiting from treatment at the end the primary study and have not experienced any unacceptable safety issues.

4.4 Stopping Rules, Discontinuation and Withdrawal Criteria and Procedures

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 8.1.5) as they are reported from the study centres to identify safety concerns. A specific clinical site or a given cohort can be discontinued or the entire study may be terminated at any time if the Sponsor judges it necessary for any reason. In such case, all scheduled procedures and assessments for participants who are still in the study will be performed. Some possible reasons for the closure of a study site may include:

- Failure of the Investigator staff to comply with the protocol or with the GCP guidelines
- Safety concerns
- Inadequate participant recruitment.

In case of premature discontinuation of a clinical site or the complete study, depending on the reason(s) for the discontinuation, the Sponsor will inform the Investigator(s) affected in writing as to whether the ongoing participants should receive the remaining triptorelin dose administration(s).

A participant or the parent(s)/legal guardian of the participant may prematurely discontinue participation in the study at any time and for any reason, including:

- Drug-related AE
- Non-drug related AE
- Non-drug related reason, e.g. participant relocates
- Lack of efficacy
- Withdrawal of consent (participant's decision).

The Investigator and/or Sponsor can withdraw a participant from the study at any time for any reason (e.g. protocol violation or deviation as defined in Section 13.1.2, non-compliance with the protocol conditions, AEs, participant does not receive any of the triptorelin injections planned in the protocol, participant lost to follow-up). All cases of discontinuation will be discussed between the Investigator and the Sponsor.

If a participant decides to withdraw from the study after administration of triptorelin, or should the Investigator decide to withdraw the participant, 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 participant's withdrawal should be made (see Section 5.2.3 and Table 1, for participants entered in the extension phase should refer to Table 2) and an explanation given as to why the participant is withdrawing or being withdrawn from the study.

The reason for withdrawal and date of withdrawal from the study must be recorded on the eCRF. If a participant 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 participant is referred to the care of a local health care professional, or until a determination of a cause unrelated to triptorelin 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, at the EOS visit. If the EOS visit is conducted outside the window after the final triptorelin dose

(Table 1, refer to Table 2 for the extension phase), all safety evaluations will be performed but efficacy evaluations will not be made.

4.5 Temporary Discontinuation

In case of suspected or confirmed COVID-19 (SARS-CoV-2) infection, the intervention administration may be temporarily discontinued depending on the participant's clinical presentation. In some cases, the investigator may request a participant be retested before the intervention administration is resumed.

4.6 Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The site should counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, three telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

4.7 Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes date of informed consent, demography, reason for screen failure, eligibility criteria and any SAE.

5 STUDY PROCEDURES

5.1 Study Schedule

If the COVID-19 pandemic prevents participants from coming to the site, participants can have their study visit assessments performed remotely as judged appropriate by the Investigator. This must be discussed with the Sponsor before being implemented. In such a case, the Investigator will perform a telemedicine visit and will make every effort, where applicable, to contact the participant's general practitioner or specialist physician to ensure all important medical information and safety event(s) occurring since the last visit are collected. Guidance on how to collect protocol-planned assessments will be provided to the Investigator in a separate document. Such document will be filed in the trial master file. The IEC/IRBs will be notified of the changes as applicable locally. Of note, as the adapted visit deviates from the regular protocol plan, the changes will be recorded as protocol deviations related to COVID-19.

Main study

The schedule of procedures and assessments to be performed during the study is summarised in Table 1.

Table 1 Schedule of Assessments

	Screening Visit		Month 3	Month 6
	Day -28 to Day -1 Prior to Treatment	Day 1	Day 91	Day 182 (EOS/Early Withdrawal)[t]
Study procedures [a]			±3 days	±3 days
Informed consent/assent [b]	X			
Eligibility check [c]	X	X		
Demography	X			
Medical and surgical history	X			
PK samples[d]		X	X	X
Basal LH and FSH [e]	X		X	X
GnRH test with samples for LH and FSH [f]	X		X	X
Oestradiol or testosterone samples [g]	X		X	X
Pubertal Stage (Tanner method) [h]	X			X
Auxological parameters [i]	X		X	X
Bone age and chronological age [j]	X			X
Gonad development [k]	X			X
Body weight [l]	X		X	X
Adverse events [m]	X	X	X	X
Pregnancy test [n]	X			X
Clinical laboratory tests [o]	X		X	X
Physical examination and vital signs [p]	X	X	X	X
Prior and concomitant medications [q]	X	X	X	X
Study drug administration [r]		X	X	
Local tolerability [s]		X	X	

BMI=Body mass index; eCRF=electronic case report form, EOS=End of Study; FSH=Follicle-stimulating hormone; GnRH=Gonadotropin-releasing hormone; IEC=Independent Ethics Committee; IRB=Institutional Review Board; LH=Luteinising hormone; PK=pharmacokinetic

Footnotes to Schedule of Assessments

a **Study procedures** to be done before dosing except local tolerability and post-dose PK

b **Informed consent/assent** to be performed by parent/legal guardian and by children if determined by local IRB/IEC requirements.

c **Eligibility check** of inclusion and exclusion criteria to occur at Screening and prior to dosing on Day 1. All subjects should receive brain MRI to confirm CPP and check for tumours at screening, unless they have available brain MRI scans within 6 months for site to verify.

d **PK Samples** on Day 1 to be taken predose and at 4 hours post-injection (±2-hour window); PK sample at Month 3 visit to be taken predose; PK sample at the Month 6 EOS/early withdrawal visit.

e **Basal LH and FSH** samples to be drawn before GnRH test. Blood sampling should be taken at approximately the same time of day during each visit.

f **GnRH test** samples for LH and FSH concentrations will be collected at 30, 60 and 90 minutes (±5 minutes at each timepoint) after the GnRH test. The LH and FSH samples will all be taken before injection of triptorelin, if applicable (e.g. Month 3 visit).

g **Oestradiol and Testosterone** samples for girls and boys, respectively.

h **Tanner pubertal stage** as defined in Appendix 1.

i **Auxological parameters** including height, growth velocity, weight, BMI will be assessed.

j **Bone Age** by Greulich and Pyle method.

k **Gonad development** uterine length in girls or testicular volume in boys assessed by type B ultrasound.

l **Body weight** participants should weigh ≥20 kg on inclusion in the study.

m **Adverse events** will be collected up to and including the Month 6 visit (i.e. Day 182±3 days)

n **Pregnancy test** for female participants only. Girls who have entered menarche must have a negative pregnancy test prior to the start of study treatment and should not be at risk of pregnancy throughout the study period. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC before drug treatment for all female participants of childbearing potential and if clinically indicated thereafter.

o **Clinical laboratory** tests including chemistry, haematology and urinalysis. In case of abnormal blood glucose as per Investigator's judgement, repetition of these tests will be performed before the first injection.

p **Physical examination and vital signs** blood pressure and heart rate.

q **Prior and concomitant medications** assessed at every visit

r **Study drug administration** following all other assessments, apart from PK samples on Day 1.

s **Local tolerability** Measured by tenderness, redness, bruising, erythema, swelling, rash, pain, itching, induration, haematoma, ulceration or necrosis. To be assessed at injection and 2 hours post injection.

t **EOS/Early Withdrawal** For participants who do not have a final visit within 3 months (i.e. up to Day 182±3 days) after their last triptorelin dose, efficacy evaluations (including PK sampling) will not be performed. Data from any efficacy evaluations performed after this time will not be collected on the eCRF.

Extension phase

The schedule of procedures and assessments to be performed during the extension study is summarised in Table 2.

Table 2 Schedule of Assessments in Extension Phase

	Extension phase Baseline	Month 9	Month 12
	Day 1 (day 182 - Month 6)	Day 271	Day 365 (EOEP/Early Withdrawal) [h]
Study procedures [a]		±3 days	±3 days
Informed consent/assent [a]	X		
Basal LH and FSH		X	X
GnRH test with samples for LH and FSH [b]			X
Oestradiol or testosterone samples		X	X
Pubertal Stage (Tanner method)			X
Auxological parameters [c]		X	X
Bone age and chronological age [d]			X
Gonad development [e]			X
Adverse events	X	X	X
Pregnancy test			X
Clinical laboratory tests [f]		X	X
Physical examination and vital signs		X	X
Prior and concomitant medications		X	X
Study drug administration	X	X	
Local tolerability [g]	X	X	

BMI=Body mass index; eCRF=electronic case report form, EOEP=End of Extension Phase; FSH=Follicle-stimulating hormone; GnRH=Gonadotropin-releasing hormone; IEC=Independent Ethics Committee; IRB=Institutional Review Board; LH=Luteinising hormone

Footnotes to Schedule of Assessments

a **Informed consent/assent** to be performed by parent/legal guardian and by children if determined by local IRB/IEC requirements.

b **GnRH test** samples for LH and FSH concentrations will be collected at 30, 60 and 90 minutes (±5 minutes at each timepoint) after the GnRH test. The LH and FSH samples will all be taken before injection of triptorelin, if applicable.

c **Auxological parameters** including height, growth velocity, weight, BMI will be assessed.

d **Bone Age** by Greulich and Pyle method.

e **Gonad development** uterine length in girls or testicular volume in boys assessed by type B ultrasound.

f **Clinical laboratory** tests including chemistry, haematology and urinalysis.

g **Local tolerability** Measured by tenderness, redness, bruising, erythema, swelling, rash, pain, itching, induration, haematoma, ulceration or necrosis to be assessed at injection.

h **EOEP/Early Withdrawal** For participants who do not have a final visit within 3 months (i.e. up to Day 365+3 days) after their last triptorelin dose, efficacy evaluations will not be performed. Data from any efficacy evaluations performed after this time will not be collected on the eCRF.

5.2 Study Visits

For a detailed list of procedures at each visit, see Table 1 and Table 2.

5.2.1 Procedures for the Screening Visit (Day -28 to Day -1 Prior to Treatment) and Enrolment

A signed and dated informed consent form will be obtained from each parent/legal guardian and a signed and dated assent form will be obtained from each participant before any screening procedures, according to local IRB/IEC requirements. Evaluations obtained as part of routine medical care and performed during the Screening period may be used in place of the study-specific evaluations. Parents/legal guardians will acknowledge and agree to the possible use of this information for the study by giving informed consent.

After informed consent is obtained, screened participants will be allocated a participant number. All screened participants must be identifiable throughout the study. The Investigator will

maintain a list of participant numbers and names to enable records to be found at a later date if required. Each Investigator will also maintain a record of all participants screened in the study (i.e. who signed the informed consent form).

Under no circumstances will participants be screened more than once.

Following confirmation of eligibility for the study, participants will be given a treatment number.

The participant's eligibility for the study will be checked at the Screening visit (based on the inclusion and exclusion criteria presented in Section 4.1 and Section 4.2, respectively) and the assessments described in Table 1 will be performed.

5.2.2 Procedures During the Treatment Phase of Study (Day 1 and Month 3)

The participant's eligibility for the study will be checked again at Day 1 visit (based on the Inclusion and Exclusion criteria presented in Section 4.1 and 4.2, respectively) before the other assessments listed in Table 1.

Participants will be admitted at the clinical site on the morning of Day 1 and the Month 3 visit and the assessments described in Table 1 will be performed. Study drug administration will follow after the other assessments, apart from any post-dose PK samples and local tolerability.

5.2.3 Procedures Following Study Treatment (Month 6, End of Main Study or Early Withdrawal Visit)

Participants who complete the main study will perform final procedures and assessments at the final visit (Month 6). Participants who withdraw from the study before the completion of the evaluation period will be invited to attend an Early Withdrawal visit to perform early discontinuation procedures and assessments (as in Table 1).

For participants who do not have a final visit within 3 months (i.e. up to Day 182±3 days as in Table 1) after their last triptorelin dose, efficacy evaluations should not be performed. Data from any efficacy evaluations performed after this time will not be collected on the eCRF.

Participants with ongoing AEs or clinically significant laboratory test abnormalities (as determined by the Investigator) will be monitored as described in Section 8.1.4 and Section 8.1.2.4, respectively. The AEs will be collected up to 3 months after the date of the last injection.

5.2.4 Procedures During the Extension Phase (Month 6, Month 9 and End of Extension Phase Visit)

At the end of the main study, participants who are still benefiting from treatment (i.e. not progressing) and who have not experienced any unacceptable safety issues, will have the option to continue to receive triptorelin every 3 months in the 6-month extension phase.

The participant's eligibility for the extension phase will be checked at Extension Phase Day 1 visit (Month 6) (based on the Inclusion criteria presented in Section 4.3, respectively). The Extension Phase Day 1 visit will correspond to the End of main Study Visit.

Participants will be admitted at the clinical site on the morning of Month 6, Month 9 and Month 12 visit and the assessments described in Table 2 will be performed. Study drug administration will follow after the other assessments on the Month 6 and Month 9 visits, apart from any post-dose PK samples and local tolerability.

For participants who do not have a final visit within 3 months (i.e. up to Day 365±3 days as in Table 2) after their last triptorelin dose, efficacy evaluations should not be performed. Data from any efficacy evaluations performed after this time will not be collected on the eCRF.

5.3 Laboratory Assessments

All efficacy parameters listed below (i.e. LH, FSH, testosterone and oestradiol), and samples for triptorelin PK, will be analysed centrally. The preparation and storage of samples are described separately in the Laboratory Manual. Laboratory safety tests will be conducted locally.

At Day 1 visit, in case of abnormal blood glucose as per Investigator's judgement, repetition of this test will be performed before the first triptorelin injection.

The following laboratory parameters will be analysed from samples collected at timepoints described in Table 1:

(1) LH and FSH concentrations at baseline and after GnRH stimulation (this analysis will be conducted as described in the Laboratory Manual);

(2) Oestradiol and testosterone levels;

(3) Pregnancy test (only in female participants with childbearing potential), Section 8.1.6;

(4) Haematology (complete blood count (CBC)), Section 8.2.1;

(5) Blood chemistry such as creatinine and glucose, Section 8.2.2;

(6) Liver function tests, including ALT, AST, alkaline phosphatase (ALP) and bilirubin, Section 8.2.2;

(7) Urinalysis (pH, protein, ketones, bilirubin, blood, urobilinogen, nitrites, leukocytes, glucose and specific gravity by dipstick), Section 8.2.3;

(8) Pharmacokinetic concentrations, Section 9.1.

6 TREATMENT OF PARTICIPANTS

6.1 Investigational Medicinal Product Preparation, Storage, Security and Accountability

6.1.1 Investigational Medicinal Product Storage and Security

The Investigator or an approved representative (e.g. pharmacist) will ensure that all triptorelin and any other study-related material are stored in a secured area, under recommended temperature-monitored storage conditions, in accordance with applicable regulatory requirements.

Triptorelin must be stored in the outer carton at a temperature below 25°C, protected from freezing.

At the clinical site(s), triptorelin must only be dispensed by the Investigator or by a member of staff specifically authorised by the Investigator and trained for triptorelin reconstitution and administration.

Batch and kit number of each administered triptorelin kit will be recorded in the eCRF.

6.1.2 Investigational Medicinal Product Preparation

The Investigator or an approved representative (e.g. pharmacist) will ensure that triptorelin is reconstituted and dispensed by a member of staff specifically authorised by the Investigator and trained for triptorelin reconstitution and administration.

The suspension for injection must be reconstituted using an aseptic technique and using the ampoule of solvent supplied for injection.

The instructions for reconstitution hereafter and in the IMP Handling Manual must be strictly followed.

The solvent should be drawn into the syringe provided using the reconstitution needle (20G, without safety device) and transferred to the vial containing the powder. The suspension should be reconstituted by swirling the vial in a gentle circular motion until a homogeneous, milky suspension is formed. Do not invert the vial.

It is important to check there is no unsuspended powder in the vial. The suspension obtained should then be drawn back into the syringe, without inverting the vial. The reconstitution needle should then be changed and the injection needle (20G, with safety device) used to administer the product.

As the product is a suspension, the injection should be administered for a single use **immediately** after reconstitution to prevent precipitation.

6.1.3 Investigational Medicinal Product Accountability

Triptorelin supplies and any other study-related material are to be accounted for on the triptorelin 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 triptorelin accountability log.

Unused triptorelin or study-related material must not be discarded or used for any purpose other than the present study. Throughout the study, the monitor will collect the triptorelin accountability forms along with any unused triptorelin supplies and empty vials, in their original packs.

6.2 Study Drugs Administered

6.2.1 Triptorelin 3-Month Formulation

The study drug is a PR formulation of triptorelin 3-month formulation in a D,L-lactide-co-glycolide polymer for single i.m. injection.

At the Screening visit, participants will be allocated a participant number. On Day 1 of the study, following confirmation of eligibility for the study, all participants will receive an i.m. injection of the triptorelin 3-month formulation in the upper outer quadrant of either the right or left buttock. This injection should be done relatively rapidly and in an uninterrupted manner in order to avoid any potential blockage of the needle and will be administered preferably between 7:00 and 9:00 am. The same procedure will be followed, as closely as is feasible, at the Month 3 visit, and the Month 6 and Month 9 visits if the participant has entered the extension phase, when participants receive the triptorelin injection.

The triptorelin 3-month formulation is presented in the form of a slightly yellow freeze-dried cake or powder supplied in a single 4 mL glass vial. Two mL of a 0.8% aqueous solution of mannitol in a clear glass 2 mL ampoule is provided as the solvent for suspension. The composition of study drug and solvent ampoule is presented in Table 3 and Table 4, respectively.

Table 3 Composition of Triptorelin Pamoate 3-Month Formulation

Ingredients	Quantity (mg)	Function	Reference to Standards
Active Substance			
Triptorelin (INN) pamoate *equivalent to pure triptorelin*	CCI	Active substance	In-house specifications
Excipients			
D,L-lactide-co-glycolide polymer		Polymeric support producing prolonged release	In-house specifications
Mannitol		Lyophilisation bulking agent	Ph.Eur.
Carmellose sodium		Dispersant and viscosity regulating agent	Ph.Eur.
Polysorbate 80		Dispersant	Ph.Eur.

INN = International non-proprietary name.

CCI

Note: Reference to Ph.Eur. means current edition of the European Pharmacopoeia.

Table 4 Composition of the Solvent for Suspension

Ingredients	Quantity (mL)	Function	Reference to standards
Mannitol	0.016	Osmolality agent	Ph. Eur.
Water for injection	2.0	Solvent	Ph. Eur.

Note: Reference to Ph. Eur. means current edition of the European Pharmacopoeia.

6.3 Concomitant Medication/Therapy

Any prior or concomitant therapy or medication given to a participant within 2 months before triptorelin administration or during triptorelin administration will be recorded on the eCRF. Dose and generic name or trade name will be indicated.

The following concomitant medications/procedures are not permitted during this study:

- Any treatment or procedure with a definitive or potential effect on the metabolism or secretion of gonadotropins (LH or FSH) or sex steroids (oestradiol and/or testosterone) will be considered as a protocol violation;
- All drugs mentioned as prohibited in the exclusion criteria remain prohibited during the study period: GnRH analogues (other than triptorelin 3-month formulation), medroxyprogesterone acetate, growth hormone or IGF-1, systemic or inhaled steroids (mild topical steroids are permitted), anticoagulants (heparin and coumarine derivatives).
- Any concurrent investigational agent or procedure.

6.4 Lifestyle Restrictions/Recommendations

In addition to the restrictions already presented in the exclusion criteria (see Section 4.2), from 48 hours prior to Day 1 and until the EOS visit participants will also be requested to avoid the following:

- Strenuous physical activity;
- Poppy-seed consumption.

6.5 Procedures for Monitoring Participant Compliance

The Investigator will be responsible for monitoring participant compliance. Participants may be withdrawn from the study at any time if the Investigator or the Sponsor determines that the participant is not in compliance with the study protocol (see Section 4.4 for details).

When participants are dosed at the site, they will receive triptorelin directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the site will be recorded in the source documents and in the CRF. The dose of triptorelin and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the injection.

7 ASSESSMENT OF EFFICACY

In this study, efficacy will be assessed by measuring LH, FSH, oestradiol and testosterone concentrations, pubertal stage, auxological parameters, BA, CA and gonad development.

For the timing of assessments, please refer to the schedule in Table 1 and Table 2.

7.1 Primary Efficacy Endpoint and Evaluation

The primary endpoint in this study is the proportion of children with LH suppression defined as stimulated peak LH ≤3 IU/L after GnRH stimulation at Month 3. The GnRH stimulation test is performed by using an i.v. injection of gonadorelin (synthetic GnRH) to stimulate gonadotrophin release and blood samples will be collected prior to and 30, 60 and 90 minutes after the gonadorelin injection for central assessment of serum LH levels.

7.2 Secondary Efficacy Endpoints and Evaluations

Secondary efficacy endpoints and evaluations are summarised in Table 5. For this study, baseline values correspond to those obtained with measurements performed at the Screening visit.

Table 5 Secondary Efficacy Endpoints and Evaluations

Measure	Timepoint	Variable	Endpoint
Basal LH and FSH serum levels	Baseline, Month 3 and Month 6 (EOS)	LH and FSH concentration	Change in basal serum LH and FSH levels at Month 3 and Month 6 compared to baseline
Peak LH after GnRH stimulation test	Baseline, Month 3 and Month 6 (EOS)	Peak LH levels after GnRH stimulation (30, 60 and 90 minutes)	Change in peak LH levels after GnRH stimulation test at Month 3 and Month 6 compared to baseline; Proportion of children with LH suppression defined as stimulated peak LH ≤3 IU/L after GnRH stimulation at Month 6.
Peak FSH levels after GnRH stimulation test	Baseline Month 3 and Month 6 (EOS)	Peak FSH levels after GnRH stimulation (30, 60 and 90 minutes)	Change in peak FSH levels after GnRH stimulation test at Month 3 and Month 6 compared to baseline.
E_2 and testosterone serum concentrations	Baseline, Month 3 and Month 6 (EOS)	Sex steroids levels	Proportion of children with sex steroids suppressed within prepubertal ranges (E_2 ≤20 pg/mL in girls and testosterone ≤0.3 ng/mL in boys); Change in sex steroids levels compared to baseline
Pubertal stage (Tanner Method)	Baseline, Month 6 (EOS)	Pubertal stage	Change in pubertal stage (genital stage in boys, breast stage in girls and pubic hair stage in both sexes) compared to baseline; Proportion of children with stabilised pubertal stage compared to baseline
Auxological parameters (height, growth velocity, weight, BMI)	Baseline, Month 3 and Month 6 (EOS)	-	Change in auxological parameters compared to baseline

Measure	Timepoint	Variable	Endpoint
BA	Baseline, Month 6 (EOS)	-	Change in BA, difference between BA and CA compared to baseline
Uterine length or testis volume	Baseline, Month 6 (EOS)	Gonad development	Change in uterine length in girls and testicular volume in boys compared to baseline

BA = Bone age; BMI = Body mass index; CA = Chronological age; EOS = End of Study; FSH = Follicle-stimulating hormone; GnRH = Gonadotropin-releasing hormone; LH = Luteinising hormone; E_2 = Oestradiol.

7.3 Extension Phase Endpoints and Evaluations

The efficacy endpoints and evaluations in the extension phase are summarised in Table 6.

Table 6 Efficacy Endpoints and Evaluations in the Extension Phase

Measure	Timepoint	Variable	Endpoint
Basal LH and FSH serum levels	Baseline, Month 9 and Month 12 (EOEP)	LH and FSH concentration	Change in basal serum LH and FSH levels at Month 9 and Month 12 compared to baseline
Peak LH after GnRH stimulation test	Baseline and Month 12 (EOEP)	Peak LH levels after GnRH stimulation (30, 60 and 90 minutes)	Change in peak LH levels after GnRH stimulation test at Month 12 compared to baseline; Proportion of children with LH suppression defined as stimulated peak LH ≤3 IU/L after GnRH stimulation at Month 12.
Peak FSH levels after GnRH stimulation test	Baseline and Month 12 (EOEP)	Peak FSH levels after GnRH stimulation (30, 60 and 90 minutes)	Change in peak FSH levels after GnRH stimulation test at Month 12 compared to baseline.
E_2 and testosterone serum concentrations	Baseline, Month 9 and Month 12 (EOEP)	Sex steroids levels	Proportion of children with sex steroids suppressed within prepubertal ranges (E_2 ≤20 pg/mL in girls and testosterone ≤0.3 ng/mL in boys); Change in sex steroids levels compared to baseline
Pubertal stage (Tanner Method)	Baseline, Month 12 (EOEP)	Pubertal stage	Change in pubertal stage (genital stage in boys, breast stage in girls and pubic hair stage in both sexes) compared to baseline; Proportion of children with stabilised pubertal stage compared to baseline
Auxological parameters (height, growth velocity, weight, BMI)	Baseline, Month 9 and Month 12 (EOEP)	-	Change in auxological parameters compared to baseline
BA	Baseline, Month 12 (EOEP)	-	Change in BA, difference between BA and CA compared to baseline

Measure	Timepoint	Variable	Endpoint
Uterine length or testis volume	Baseline, Month 12 (EOEP)	Gonad development	Change in uterine length in girls and testicular volume in boys compared to baseline

BA = Bone age; BMI = Body mass index; CA = Chronological age; EOEP = End of Extension Phase; FSH = Follicle-stimulating hormone; GnRH = Gonadotropin-releasing hormone; LH = Luteinising hormone; E_2 = Oestradiol.

7.4 Methods and Timing of Assessing, Recording and Analysing Efficacy Data

Laboratory tests for efficacy will be performed centrally. The laboratory methods for assessing efficacy data are listed in Section 5.3. The timing of efficacy assessments is summarised in Table 1. Procedures for recording efficacy data are discussed in Section 15.1 and methods of analyses are discussed in Section 11.4.4.

7.4.1 Change in Luteinising Hormone and Follicle-stimulating Hormone Serum Concentrations

These parameters will be analysed centrally, as indicated in Section 5.3. The preparation and storage of samples are described separately in the Laboratory Manual.

7.4.2 Gonadotropin-releasing Hormone Stimulation Test

Gonadorelin, a synthetic GnRH (manufacturer to be defined), will be used for gonadotrophin stimulation. Gonadorelin used for GnRH stimulation test will be prepared by the investigator sites.

Blood samples will be collected prior to gonadorelin injection (timepoint T0) and at 30 minutes (T30), 60 minutes (T60) and 90 minutes (T90) (±5 minutes at each timepoint) after a single i.v. injection of gonadorelin with 2.5 µg/kg (maximum 100 µg).

A suppressed LH response to GnRH stimulation test is defined as peak LH ≤3 IU/L among the four timepoints (T0, T30, T60 and T90).

The FSH response to GnRH stimulation will be the peak FSH level among the four timepoints (T0, T30, T60 and T90).

7.4.3 Change in Sex Steroids (Oestradiol and Testosterone Serum Concentrations)

These parameters will be analysed centrally, as indicated in Section 5.3. The preparation and storage of samples are described separately in the Laboratory Manual.

7.4.4 Change in Pubertal Stage Using the Tanner Method

See Pubertal Stages According to the Tanner Method (Appendix 1) for details.

7.4.5 Auxological Parameters, Bone Age and Chronological Age Measurements and Gonad Development

Bone age determination (in years and months) will be performed by X-rays of the hand and wrist and estimated by the Greulich and Pyle method [Greulich 1959].

Gonad development (uterine length or testis volume) will be determined by type B ultrasound.

8 ASSESSMENT OF SAFETY

8.1 Adverse Events

All AEs will be monitored from the time the participant gives informed consent until the EOS visit, or EOEP visit for those enrolled in the extension phase, (see Section 3.8 for definition of the study duration) and will be elicited by direct, non-leading questioning. Further details about AE reporting can be found in Section 8.1.2.

8.1.1 Definition of an Adverse Event

These definitions include events occurring from the time the participant gives informed consent until the end of the study (as defined in Section 3.8).

AE Definition:

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition:

- Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e. not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Event NOT Meeting the AE Definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

8.1.2 Categorisation of Adverse Events

8.1.2.1 Intensity Classification

All AEs will be recorded and graded according to the current version of the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0. In view of meta-analyses and for conversion purposes, the following conversion mapping will apply if the NCI-CTCAE scale is not available for a given AE:

- NCI-CTCAE Grade 1 corresponds to mild;
- NCI-CTCAE Grade 2 corresponds to moderate;
- NCI-CTCAE Grade 3 corresponds to severe;
- NCI-CTCAE Grade 4 corresponds to life threatening/disabling;
- NCI-CTCAE Grade 5 corresponds to death (related to AE).

Where:

- **Mild**: symptoms do not alter the participant's normal functioning;
- **Moderate**: symptoms produce some degree of impairment to function but are not hazardous, uncomfortable or embarrassing to the participant;
- **Severe**: symptoms definitely hazardous to wellbeing or causing significant impairment of function or incapacitation;
- **Life-threatening**: any event that places the participant at immediate risk of death from the event as it occurred, i.e. it does not include a reaction that, had it occurred in a more severe form, might have caused death (also see Section 8.1.5).

8.1.2.2 Causality Classification

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

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

8.1.2.3 Assessment of Expectedness

The reference document for assessing expectedness of AEs in this study will be the current IB.

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 the schedule of triptorelin administration (change in dosage, delay in administration, study drug discontinuation);
- They require intervention or a diagnostic evaluation to assess the risk to the participant;
- They are considered clinically significant by the Investigator;

- They are serious.

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 Local Tolerability Abnormalities

During local tolerability assessment after each triptorelin injection, any new or worsening local reactions **deemed clinically significant by the Investigator** must be reported as an AE in the AE page of the eCRF, including start and stop dates, intensity, seriousness and action taken with study treatment.

8.1.2.7 Other Investigation Abnormal Findings

Abnormal test findings judged by the Investigator as clinically significant that result in a change in study drug dosage or administration schedule, or in discontinuation of the study drug, or require intervention or diagnostic evaluation to assess the risk to the participant, should be recorded as AEs.

8.1.3 Adverse Events of Special Interest

Not applicable.

8.1.4 Recording and Follow-up of Adverse Events

At each visit, the participant should be asked a non-leading question such as: "How have you felt since last dose/the last assessment?".

All observed or volunteered AEs, regardless of treatment group or suspected causal relationship to triptorelin, will be recorded in the AE page(s) of the eCRF. Events involving drug and/or local tolerability reactions, accidents, illnesses with onset during the treatment phase of the study, or exacerbations of pre-existing illnesses will be recorded as AEs.

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

For all AEs, the Investigator must pursue and obtain adequate information both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an 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. triptorelin or other reason). The Investigator is required to assess causality and record that assessment on the eCRF. Follow-up of the AE, after the date of triptorelin 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.

8.1.5 Reporting of Serious Adverse Events

All SAEs (as defined below), regardless of treatment group or suspected relationship to triptorelin, must be reported immediately (within 24 hours of the Investigator's knowledge of the event) using the SAE report form via the email address or the fax number specified at the beginning of this protocol as well as recording them in the eCRF.

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

(1) Results in death

(2) Is life threatening. The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe

(3) Requires in-patient hospitalisation or prolongation of existing hospitalisation.

In general, hospitalisation signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE

(4) Results in a persistent or significant disability/incapacity. The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza and accidental trauma (e.g. sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

(5) Results in congenital anomaly/birth defect in the offspring of a participant who received the triptorelin

(6) Is an important medical event that may not result in death, be life threatening, or require hospitalisation but, based upon appropriate medical judgement, may jeopardise the participant 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.

Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

A suspected or confirmed coronavirus COVID-19 (SARS-CoV-2) infection must be reported as serious (seriousness criteria should be "other medically significant" if no other seriousness criteria are present (e.g. hospitalisation).

- **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 for the 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, TEAEs (i.e. not associated with the development of a new AE or worsening of a pre-existing condition) may meet the 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 participant'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 that meet the criteria for seriousness described above.

Any SAE must be reported immediately (within 24 hours), using the SAE report form via the email address or the fax number specified at the beginning of this protocol as well as recording them in the eCRF, 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 triptorelin administration occurring at any other time after completion of the study must be reported promptly, within 24 hours.

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

- Study number
- Centre number
- Participant 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 the foremost untoward medical occurrence from secondary AEs that occurred as complications.

8.1.6 Pregnancy

Information regarding pregnancies must be collected as an SAE on the AE page of the eCRF and reported to the Sponsor within 24 hours as described in Section 8.1.5.

If pregnancy occurs during the study, the outcome of the pregnancy will be collected following completion of the study. The Sponsor will request further information from the Investigator as to the course and outcome of the pregnancy using the Standard Drug Exposure for Pregnancy Form.

The Investigator must instruct all female participants who have already had menophania/menarche to inform them immediately should they become pregnant during the study. The Investigator should counsel the participant, discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the participant should continue until conclusion of the pregnancy, which may involve follow-up after the participant's involvement in the study has ended.

Pregnancies with a conception date within 3 months after the participant's last dose of study medication must also be reported to the Investigator for onward reporting to the Sponsor.

If the Investigator becomes aware of a pregnancy occurring in the partner of a participant participating in the study, this should be reported to the Sponsor as described above. Pregnancies in the partner with a conception date until 3 months after participant's last dose of

study medication should be reported after the partner has given written consent and the partner should be counselled and followed as described above. Monitoring of the partner should continue until conclusion of the pregnancy.

8.1.7 Deaths

All AEs resulting in death during the study period (from first injection until 3 months after the date of the last study drug administration), 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 (e.g. multiple organ failure, pneumonia, myocardial infarction)
- 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 reported as "death" or "sudden death".

8.1.8 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 triptorelin (see Section 4.4).

If triptorelin is discontinued due to an SAE, it must be reported immediately to the Sponsor's designated representative (see Section 8.1.5).

In all cases, the Investigator must ensure that the participant receives appropriate medical follow-up (see Section 8.1.4).

8.1.9 Reporting to Competent Authorities/Independent Ethics Committees/Institutional Review Boards/Other Investigators

The Sponsor will ensure that processes are in place for the submission of reports of suspected unexpected serious adverse reactions (SUSARs) occurring during the study to the competent authorities, IECs and other Investigators involved with triptorelin. Reporting will be in accordance with the applicable regulatory requirements.

8.2 Clinical Laboratory Tests

Blood and urine samples will be collected as per Table 1 and Table 2 for the evaluation of haematology, serum chemistry 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 (volume to be collected as per local laboratory manual) will be collected in a potassium ethylenediaminetetraacetic acid tube to assess CBC.

8.2.2 Blood Chemistry

Blood samples (volume collected as per local clinical practice) will be collected in an activator gel tube to assess the following parameters:

- Creatinine

- Glucose
- ALT
- AST
- ALP
- Bilirubin.

In the case of abnormal blood glucose as per Investigator's judgement, repetition of these tests will be performed before the first triptorelin injection.

8.2.3 Urinalysis

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

Microscopy will be performed, if indicated, but results will not be collected in the eCRF. If in the opinion of the Investigator there are any clinically significant abnormalities in microscopy, they will be recorded as an AE in the eCRF.

8.2.4 Pregnancy Test

Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC before drug treatment for all female participants of childbearing potential and if clinically indicated thereafter. Any participant becoming pregnant during the study will be withdrawn. All pregnancies that occur during the study are to be reported as described in Section 8.1.6.

8.2.5 Other Clinical Laboratory Tests

Other clinical laboratory tests will be performed to ensure the safety of the participants but will not be an assessment of the safety of the study drug.

8.3 Physical Examination

Physical examinations, including body weight, will be conducted at timepoints described in Table 1 and Table 2. Body weight will be measured in underwear and without shoes.

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 Local Tolerability

Assessment of local tolerability will be conducted as presented in the schedule of assessments (Table 1 and Table 2) and as described in this section.

After each triptorelin injection, the injection site will be examined, at injection and 2 hours post injection, by a physician or medical research associate and assessed for characteristics such as but not limited to tenderness, redness, bruising, erythema, swelling, rash, pain, itching, induration, haematoma, ulceration or necrosis. If present, the extent of erythema, haematoma, rash, ulceration or necrosis will be described and assessed quantitatively; this will at least include measurement of maximum length and maximum width.

Any reaction deemed clinically significant by the Investigator meets the definition of a TEAE, thus it needs to be reported in the eCRF as such, as indicated in Section 8.1.2.6.

8.5 Vital Signs

Blood pressure and heart rate will be assessed at timepoints described in Table 1 and Table 2 with an automated device so that measurements are independent of the observer. Blood pressure and heart rate will be recorded in sitting position after 5 minutes of rest (seated). Absolute values and change from baseline will be analysed.

9 ASSESSMENTS OF PHARMACOKINETICS/PHARMACODYNAMICS

9.1 Pharmacokinetics

Sparse PK samples (triptorelin), will be taken in all participants as described in Table 1.

9.1.1 Sample Collection

Blood samples for the assay of triptorelin will be collected in Vacutainer tubes at the timepoints indicated in Table 1. 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 bioanalytical CRO 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 bioanalytical CRO, samples will be checked and stored until analysis.

9.1.2 Analytical Procedures

The concentration of triptorelin will be analysed using a validated specific and sensitive method, and in accordance with Good Laboratory Practice (GLP). All details of sample collection, handling, shipment, methodology and reference ranges will be provided in the Study Manual and archived in the Trial Master File.

9.1.3 Data Analysis

Individual listings and summary statistics will be presented for PK concentrations.

9.2 Pharmacodynamics

Not applicable.

10 EXPLORATORY BIOMARKERS AND BIOBANKING

There are no exploratory biomarkers or biobanking planned for this study.

Note that a description of primary and secondary efficacy biomarkers can be found in Section 3.2.

11 STATISTICS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), to be approved before the first participant enters the study. The SAP may include changes to the plans outlined in this protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

Statistical evaluation will be performed using Statistical Analysis System (SAS®) Version 9.4 (or higher if available).

11.1 Analysis Populations

The following populations will be used during statistical analyses:

- **Screened population**: All participants screened (i.e. who signed the informed consent)
- **Safety population**: All participants who received at least one dose of study medication and have at least one post-baseline safety assessment
- **Intention-To-Treat population (ITT)**: All participants who received at least one dose of study medication
- **Modified Intention-To-Treat population (mITT):** All treated participants having at least one baseline and at Month 3 post-baseline assessment of the primary efficacy endpoint
- **Per protocol (PP) set**: All participants in the mITT after exclusion of the participants who had major protocol deviations that could potentially affect the primary efficacy endpoint outcome for the participants
- **PK set:** All participants who received at least one dose of study medication and have at least one valid and quantifiable concentration.

11.1.1 Populations Analysed

Main phase

The primary efficacy analysis will be performed on the mITT population. Supportive analysis of the primary efficacy endpoints will be based on the ITT and the PP populations.

The secondary efficacy analyses will be based on the mITT population. Supportive analysis of the secondary analyses may be performed on the PP population.

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

The analyses of PK data will be performed based on the PK population.

Extension phase

The analysis sets for the efficacy endpoints will be the ITT set and the PP set. Analyses and summary tables for the safety endpoints will be based upon the Safety population.

11.1.2 Reasons for Exclusion from the Analyses

Any major protocol deviation (see Section 13.1.2 for definition) will be described and listed and its impact on the inclusion of any participant in each analysis population will be specified. The final list of protocol deviations impacting each analysis population will be reviewed prior to database lock. The list may be updated, up to the point of database lock, to include any additional protocol deviations which may impact the analysis of each population.

11.2 Sample Size Determination

Main phase

The purpose of this study is to observe whether the effectiveness of triptorelin 3-month formulation in Chinese population of CPP children has the same or similar trend with that in

overseas CPP population, mainly using descriptive statistical analysis. Although no formal statistical testing will be carried out, the following assumptions were made, based on global pivotal study 2-54-52014-143 [Zenaty 2016], for the sample size to enable an evaluation of the trend of effectiveness:

- Expected outcome for the proportion of children with a suppressed LH response to the GnRH stimulation test (stimulated peak LH ≤3 IU/L) at Month 3 is 90%
- Null proportion is 70%
- An exact binomial test of a proportion with a one-sided nominal significance level of 0.05 and power =85%
- Expected common dropout rate =10%.

Under these assumptions, approximately 32 (28 with additional 10% dropouts) participants (Power Analysis and Sample Size (PASS) software) including three boys are planned to be enrolled into the study in order to observe the efficacy of the triptorelin 3-month formulation in the proportion of children with a suppressed LH response to the GnRH stimulation test at Month 3.

Extension phase

The number of participants included in the extension study will be dependent on the number of participants from study D-CN-52014-243 who give consent to continue into the extension study. A maximum of 32 participants will be expected to be enrolled in the extension phase.

11.3 Significance Testing and Estimations

The observed response rate in global study 2-54-52014-143 was 83.8% (95% CI: 68.0% to 93.8%). With N=28, there is 90% probability that the observed response rate will be within 16 percentage points of the true response rate based on a simulation. Due to the small sample size and potential wider precision of the estimator, the primary endpoint will be summarised descriptively. No formal hypothesis test will be performed.

For the primary efficacy endpoint, the summary statistics of number and percentage of participants and the exact two-sided 90% confidence interval (CI) for a binomial proportion will be computed by SAS® using the exact binomial distributions on the mITT (primary population of analysis), ITT and PP.

For secondary efficacy endpoints related to a change at Month 3 and Month 6 compared to baseline, the descriptive summary statistics (n, mean, SD, median, minimum, maximum) will be calculated on the mITT. In addition, secondary efficacy endpoints may be performed on the PP. Exact two-sided 90% CIs will also be constructed for all secondary endpoints expressed as percentages.

For extension phase efficacy endpoints related to a change at Month 9 and Month 12 compared to baseline, the descriptive summary statistics (n, mean, SD, median, minimum, maximum) will be calculated on the ITT and PP. Exact two-sided 90% CIs will also be constructed for all extension phase efficacy endpoints expressed as percentages.

The analysis results based on the statistical methods above will provide the reference for whether the efficacy of treatment of CPP in children in China has same or similar trend with that in overseas CPP population.

11.4 Statistical/Analytical Methods

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

11.4.1 Demographic and Other Baseline Characteristics

Descriptive summary statistics (n, mean, SD, median, minimum, maximum) and frequency counts of demographic and baseline data (medical history, concomitant disease, predosing AEs and ongoing medical history, prior and concomitant medications and therapies) will be presented for the ITT, mITT and PP, as well as the Safety population.

11.4.2 Participant Disposition and Withdrawals

The numbers and percentages of participants screened and included in each of the analysis populations will be tabulated overall and by centre. The reasons for participant exclusions from each of the populations and primary reasons for study discontinuation will be tabulated.

11.4.3 Pharmacokinetic Data

Summary statistics will be presented for triptorelin plasma concentrations. Concentrations will be compared to the historical data using a model previously developed. If required and warranted by the data, an attempt to build a model to characterize the PK in the population will be made.

11.4.4 Efficacy Evaluation (Main Phase)

11.4.4.1 Primary Efficacy Endpoint

As indicated in Section 7.1, the primary efficacy endpoint is the proportion of children with LH suppression defined as stimulated peak LH ≤3 IU/L after GnRH stimulation at Month 3. The GnRH stimulation test is performed by using i.v. injection of gonadorelin (synthetic GnRH) to stimulate gonadotrophin release, and blood samples will be collected prior to and 30, 60, 90 minutes (±5 minutes at each timepoint) after the gonadorelin injection for central assessment of serum LH levels.

11.4.4.2 Secondary Efficacy Endpoint

As indicated in Section 7.2, the secondary efficacy endpoints are the following:

- Change in basal serum LH and FSH levels at Month 3 and Month 6 compared to baseline
- Proportion of children with LH suppression defined as stimulated peak LH ≤3 IU/L after GnRH stimulation at Month 6
- Change in peak LH level after the GnRH stimulation test at Month 3 and Month 6 compared to baseline
- Change in peak FSH level after the GnRH stimulation test at Month 3 and Month 6 compared to baseline
- Proportion of children with pre-pubertal levels of sex steroids (defined as oestradiol ≤20 pg/mL in girls and testosterone ≤0.3 ng/mL in boys) at Month 3 and Month 6
- Change in oestradiol levels in girls and testosterone levels in boys at Month 3 and Month 6 compared to baseline
- Change in pubertal stage using the Tanner method (genital stage in boys, breast stage in girls and pubic hair stage in both sexes) at Month 6 compared to baseline
- Proportion of children with stabilised pubertal stage compared to baseline stage using the Tanner method at Month 6
- Change in auxological parameters including height, growth velocity, weight and BMI at Month 3 and Month 6 compared to baseline
- Change in BA, difference between BA and CA at Month 6 compared to baseline
- Change in uterine length in girls and testicular volume in boys at Month 6 compared to baseline.

11.4.4.3 Exploratory Pharmacokinetics Endpoint

- To assess sparse plasma triptorelin concentrations at Day 1, Month 3 and Month 6.

11.4.5 Adjustment for Country/Centre Effect

Descriptive analysis will be carried out to evaluate any possible centre effect.

11.4.6 Safety Evaluation (Main Phase)

Safety endpoints are indicated in Section 3.2.3.

All safety data will be included in the participant data listings. Analyses and summary tables will be based on the Safety population.

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version (version in use before database lock) and will be classified by MedDRA preferred term (PT) and system organ class (SOC). All AE listings will be presented by participant and by SOC and PT.

The incidence of all reported TEAEs, TEAEs associated with early withdrawal and SAEs will be tabulated overall. In addition, summary tables will be presented by maximum intensity and drug relationship.

A TEAE is defined as any AE that occurs during the active phase of the study (between the start date of the treatment and the end of study treatment) if:

- It was not present prior to receiving the first dose of triptorelin, or
- It was present prior to receiving the first dose of triptorelin but the grade increased or became serious during the active phase of the study, or
- It was present prior to receiving the first dose of triptorelin, the grade/seriousness is the same but the causality changed to "related" during the active phase of the study.

All TEAEs will be flagged in the AE listings.

Summary incidence tables will be provided, classified by SOC, PT and associated NCI-CTCAE worst grade. In the event of multiple occurrences of the same AEs being reported for the same participant, the maximum intensity (Grade 5 >Grade 4 >Grade 3 >Grade 2 >Grade 1 >missing >not applicable) will be chosen. All AEs will be collected up to the EOS visit (see Table 1 for schedule), or EOEP visit for those enrolled in the extension phase.

Concomitant medication will be coded by using World Health Organization Drug Dictionary (WHO-DD) version (current version in use at the start of the study) and will be summarised with the number and percentage of participants receiving concomitant medication by drug class and preferred drug name.

Haematological and biochemical toxicities will be recorded and graded according to the NCI-CTCAE criteria, where available. The NCI-CTCAE Grades 3 and 4 haematology and biochemistry variables will be listed by participant and by visit.

Actual values and changes from Baseline in clinical laboratory tests, physical examinations and vital signs will be summarised using descriptive statistics at each visit. 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 using the worst on-treatment grade will be presented for the number and percentage of participants with NCI-CTCAE grades.

11.4.7 Efficacy and Safety Evaluations (Extension Phase)

A separate analysis on efficacy and safety endpoints will be performed considering the extension phase duration, a period of an additional 6 months, lasting until the End of Extension Phase Visit at Month 12.

As this is an extension phase following the main study phase, the efficacy and safety endpoints in the extension phase will be summarised descriptively. No formal statistical hypotheses testing will be performed.

Statistical analyses will include the following:

- For the continuous endpoints, the descriptive summary statistics (number of participants (n), mean, SD, median, minimum, maximum) will be calculated
- For the categorical endpoints, the summary statistics of number and percentage of participants and the exact two-sided 90% confidence interval (CI) will be calculated.

11.4.7.1 Efficacy Endpoint

As indicated in Section 3.3.1, the extension phase efficacy endpoints are the following:

- Proportion of children with LH suppression (defined as LH ≤3 IU/L) at Month 12
- Change in basal serum LH and FSH levels at Month 9 and Month 12
- Proportion of children with pre-pubertal levels of sex steroids (defined as oestradiol ≤20 pg/mL in girls and testosterone ≤0.3 ng/mL in boys) at Month 9 and Month 12
- Change in oestradiol levels in girls and testosterone levels in boys at Month 9 and Month 12
- Change in pubertal stage using the Tanner method (genital stage in boys, breast stage in girls and pubic hair stage in both sexes) at Month 12
- Proportion of children with stabilised pubertal stage compared to baseline stage using the Tanner method at Month 12
- Change in auxological parameters including height, growth velocity, weight and BMI at Month 9 and Month 12
- Change in BA, difference between BA and CA at Month 12
- Change in uterine length in girls and testicular volume in boys at Month 12

11.4.7.2 Safety Endpoints

As indicated in Section 3.3.2, the extension phase safety endpoints are the following:

- Incidence of treatment-emergent adverse events (TEAEs) throughout the study, including local tolerability
- Change in clinical safety laboratory (blood biochemistry, haematology and urinalysis) parameters at Months 9 and 12
- Change in physical examination and vital signs (blood pressure and heart rate) measurements at each visit

11.5 Subgroup Analyses

No subgroup analysis will be performed.

11.6 Interim Analyses

No interim analysis will be performed. If an unplanned interim analysis is deemed necessary, the appropriate sponsor medical director, or designee, will be consulted to determine whether it is necessary to amend the protocol.

Three analyses are planned according to the following data cut-offs if applicable:

(1) The first analysis will be performed when all participants have completed the first 3 months of the study period. The cut-off date considered for this analysis will be the date of the last Month 3 visit for the last participant. All available data at the time of this data cut-off date will be included in this analysis. The purpose of this analysis will be the final analysis of the primary efficacy endpoint, as well as the secondary efficacy and safety analyses of the first 3 months of the study period. This analysis will not be considered as an interim analysis because the first 3 months of the study period is of primary interest.

(2) The second analysis will be performed when all participants have had the opportunity to complete the main study (Month 6). This reporting database will include all main study data for all participants enrolled into the study.

(3) The third and final analysis will be performed when the last participant completes the extension phase. The reporting database will include all extension phase data.

12 DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

Authorised personnel from external competent authorities 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 13.4 and to any other locations used for the purpose of the study in question (e.g. 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.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Protocol Amendments and Protocol Deviations

13.1.1 Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favourable opinion of the IEC/IRB, except when necessary to eliminate immediate safety concerns to the participants or when the change only involves logistics or administration.

In the event that an amendment to this protocol is required, it will be classified into one of the following three categories:

- ***Non-substantial amendments*** are those that are not considered 'substantial' (e.g. administrative changes) and as such only need to be notified to the IECs or regulatory authorities for information purposes.
- ***Substantial amendments*** are those considered 'substantial' to the conduct of the clinical study where they are likely to have a significant impact on:
  - The safety or physical or mental integrity of the participants
  - The scientific value of the study
  - The conduct or management of the study, or
  - The quality or safety of the study drug used in the study.

  Substantial amendments must be submitted to and approved by the IECs and relevant regulatory authorities, according to local regulations, prior to implementing changes.
- ***Urgent amendments*** are those that require urgent safety measures to protect the study participants from immediate hazard and as such may be implemented immediately by the Sponsor with subsequent IECs and regulatory authority notification, forthwith.

The Principal Investigator and the Sponsor will sign all protocol amendments.

13.1.2 Protocol Deviations and Exceptions

All protocol deviations will be identified and recorded by the Sponsor or Sponsor's representative. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of key study data or that may significantly affect a subject's rights, safety, or well-being.

A major protocol deviation is any significant divergence from the protocol, i.e. non-adherence on the part of the participant, the Investigator, or the Sponsor to protocol-specific inclusion/exclusion criteria, primary objective evaluation criteria and/or GCP guidelines. Generally, a protocol deviation qualifies as major if:

(1) The deviation has harmed or posed a significant or substantive risk of harm to the research participant

(2) The deviation compromises the scientific integrity of the data collected for the study

(3) The deviation is a wilful or knowing breach of participant protection regulations, policies, or procedures on the part of the Investigator(s)

(4) The deviation involves a serious or continuing non-compliance with any applicable participant protection regulations, policies, or procedures

(5) The deviation is inconsistent with the Sponsor's research, medical and/or ethical principles.

See also Section 11.1.2 for details on the impact of major protocol deviations on the inclusion of participants in each analysis population.

A minor protocol deviation is any significant divergence from the protocol that does not impact the study results.

As a matter of policy, the Sponsor will not grant exceptions to protocol-specific entry criteria to allow participants to enter the study. If under extraordinary circumstances such action is considered ethically, medically and scientifically justified for a particular participant, prior approval from the Sponsor and the responsible IRB/IEC, in accordance with the standard operating procedure (SOP), is required before the participant will be allowed to enter the study. If investigative centre personnel learn that a participant who did not meet protocol eligibility criteria was entered in the study (a protocol violation), they must immediately inform the Sponsor. Such participants will be discontinued from the study, barring exceptional instances following review and written approval by the Sponsor and the IRB/IEC, according to the applicable SOP. Retention of these participants in the study will be discussed between Sponsor and Investigator, taking into account participant safety and data reliability. The IRB/IEC will be informed if participant safety/protection is ignorantly impacted.

13.2 Information to Study Personnel

To ensure accurate, complete and reliable data, the Sponsor or its representatives will provide instructional material to the study sites, as appropriate. A study initiation visit will be conducted prior to Screening start to instruct the Investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRF and all study procedures. The Investigator is responsible for giving information about the study to all staff members involved in the study or in any element of participant management, both before starting any study procedures and during the course of the study (e.g. 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.

13.3 Study Monitoring

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

The Sponsor is responsible for monitoring these data to verify that the rights and wellbeing of participants 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 guidelines and regulatory requirements.

Sponsor-assigned monitors will conduct regular site visits. The Investigator will allow direct access to all relevant files (for all participants) and clinical study supplies (dispensing and storage areas) for the purpose of verifying entries made in the eCRF and will 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 on an ongoing basis to allow regular review by the study monitor, both remotely by 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 participant's name is revealed on a document required by the Sponsor (e.g. laboratory printouts), the name must be redacted by the site personnel, leaving the initials visible, and annotated with the participant number as identification.

13.4 Investigator's Regulatory Obligations

All clinical work under this protocol will be conducted according to ICH GCP guidelines and applicable local regulations. The Investigator must be aware that the study may be audited at any time by a quality assurance personnel designated by the Sponsor or inspected by regulatory bodies. The Investigator must adhere to ICH GCP guidelines in addition to any applicable local regulations.

If requested, the Investigator will provide the Sponsor, applicable regulatory agencies and applicable Ethics Committees (ECs) with direct access to any original source documents.

The Investigator(s) should demonstrate due diligence in recruitment and screening of potential study participants. The enrolment rate should be sufficient to complete the study as agreed upon with the Sponsor. The Sponsor should be notified of any projected delays that may impact the completion of the study.

This clinical trial will be conducted in compliance with all international laws and regulations and national laws and regulations of the country(ies) in which the clinical trial is performed, as well as any applicable guidelines.

13.5 Audit and Inspection

Authorised personnel from external competent authorities and the Sponsor's authorised Quality Assurance personnel may carry out inspections and audits (see Section 12).

13.6 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.

14 ETHICS

14.1 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 1.3).

In addition, this study will adhere to all local regulatory requirements.

Before initiating the study, the Investigator/institution must 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, participant emergency study contact cards, participant recruitment procedures (e.g. advertisements), any written information to be provided to participants 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 participant 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.

14.2 Informed Consent for Participation in the Study

- The informed consent form and any participant/assent recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws. They must be approved prior to use as described in Section 14.1.
- The investigator or his/her authorised representative will explain to the participant and their legally authorised representative the nature and objectives of the study and possible risks and benefits associated with the participation. They will answer all questions regarding the study.
- Participants and their legally authorised representative must be informed that their participation is voluntary.
- The investigator or his/her authorised representative will obtain written informed consent/assent from each participant and the legally authorised representative before any study-specific procedure is performed. The investigator will retain the original of each participant's signed informed consent/assent form.
- A copy of the signed informed consent must be provided to the participant and their legally authorised representative.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the informed consent form.
- Participants must be re-consented to the most current version of the informed consent form during their participation in the study. If changes to the informed consent do not apply to all participants, this will be communicated to the IRB/IEC with a rationale. IRB/IEC approval must be received before implementation as required by local regulations.

Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study.

14.3 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.

The following documents should be submitted to the relevant EC/IRB for review and approval to conduct the study (this list may not be exhaustive):

- Protocol/amendment(s) approved by the Sponsor
- Currently applicable IB or package labelling
- Relevant Investigator's curriculum vitae
- Participant information and informed consent document(s) and form(s)
- Participant emergency study contact cards
- Recruitment procedures/materials (advertisements), if any.

The EC(s) will review all submission documents as required and a written favourable opinion for the conduct of the study should be made available to the Investigator before initiating the study. This document must be dated and clearly identify the version number(s) and date(s) of the documents submitted/reviewed and should include a statement from the EC that they comply with GCP requirements.

The study may begin at the investigational site(s) only after receiving this dated and signed documentation of the EC approval or favourable opinion.

During the study, any update to the following documents will be sent to the EC, either for information, or for review and approval, depending on how substantial the modifications are: (1) IB; (2) reports of SAEs; (3) all protocol amendments and revised informed consent(s), if any.

At the end of the study, the EC will be notified about study completion.

14.4 Confidentiality Regarding Study Participants

The Investigator must assure that the privacy of the participants, 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, participants will be identified not by their names but by an identification code (e.g. 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.

15 DATA HANDLING AND RECORD KEEPING

15.1 Recording of Study Data

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

The Investigator must record all data relating to protocol procedures, triptorelin 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. Participant completed diaries and questionnaires will be printed or electronic.

The Investigator must, as a minimum, provide an electronic signature (e-signature) to each case report book 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.

15.2 Data Management

An EDC system will be utilised for collecting participant 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 made under the e-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's and the contracted CRO's SOPs. Prior to data being received in-house at the assigned CRO, they will be monitored at the investigational site (for further details see Section 13.3). The eCRF and other data documentation removed from the investigational 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, surgical procedures and concomitant medication terms will be performed by the contracted CRO directed by the Sponsor's Biometry group and reviewed and approved by the Sponsor. Concomitant medications will be coded using WHO-DD and AEs/medical history terms will be coded using MedDRA.

Only data from enrolled participants will be reported in the eCRFs and collected in the Sponsor's database.

For screen failure participants, only the unique participant identifier, the date of informed consent signature, the reason why the participant failed screening and the potential AEs which occurred during the screening phase will be reported in the eCRFs and collected in the Sponsor's database.

15.3 Record Archiving and Retention

During the pre-study and initiation visits, the monitor must ensure that the archiving facilities are adequate and that the archiving/retention responsibilities of the Investigator have been discussed.

Study documents should be retained for 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 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.

16 FINANCING AND INSURANCE

16.1 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 participant, 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.

16.2 Insurance, Indemnity and Compensation

The Sponsor will provide product liability insurance for all participants included in the clinical study. Where required, a hospital-specific indemnity agreement will be used.

17 REPORTING AND PUBLICATION OF RESULTS

17.1 Publication Policy

The Sponsor is committed to disclosing information about the clinical trials it sponsors. Results will be communicated at scientific meetings and all reasonable efforts must be made to seek publication in a peer-reviewed scientific journal. Specific publication concepts, including data to be covered, target congress/journal and proposed authors, should be discussed with the appropriate global publications manager and incorporated in the relevant publication plan before initiation. A dedicated publications committee, involving interested members of the study steering committee as well as the global publications manager, may be established to plan specific publications. At a minimum, summary results of this study should be posted on the relevant clinical trial registry. When the trial has been conducted by a large multicentre group, the Principal Investigator, the study Steering Committee (if applicable) and the Sponsor's responsible physician should discuss and agree upon the selection of authors for planned publications in advance. They may decide to use a group name and nominate authors on behalf of the study group. All contributing Investigators will be listed in the acknowledgements together with any others who may have contributed but not sufficiently to qualify for authorship.

Selection of authors for scientific publications will follow the International Committee of Medical Journal Editors guidelines (available from http://www.icmje.org/recommendations/browse/manuscript-preparation/preparing-for-submission.html). In particular, those named as authors, whether employed by a Sponsor's affiliate or the Sponsor, or external Investigators, 'should have participated sufficiently in the work to take public responsibility for the content'.

Authorship credit should be based on:

- Substantial contributions to the conception and design, or acquisition of data, or analysis and interpretation of data
- Drafting the article or revising it critically for important intellectual content
- Final approval of the version to be published
- Agreement to be accountable for all aspects for the work, thereby ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

All authors of a manuscript should meet all four criteria. Each author must agree to their inclusion in the list of authors. Use of professional medical writing support may be employed.

Resolution of scientific differences in the presentation or interpretation of study findings will be conducted along principles of honest scientific debate. The Sponsor shall be promptly notified of any amendments subsequently requested by referees or journal editors.

All publications arising from this study will be reviewed by relevant functions at the Sponsor, coordinated by the global publications team. Requests and suggestions for changes will be discussed with all authors (and medical writer, if applicable). Resolution of scientific differences in the presentation or interpretation of study findings will be conducted along principles of honest scientific debate. The Sponsor's review comments must be answered before a final version for submission can be approved by the author team.

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 upon 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.

17.2 Clinical Study Report

A final clinical study report (CSR) will be prepared according to the ICH and National Medical Products Administration guideline on structure and contents of CSRs. A final CSR will be prepared where any participant 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 comply with any applicable regulatory requirements, national laws in force.

If applicable, a main CSR will be written to report the primary endpoint. If required, a CSR Addendum will subsequently be added to summarise the remainder of the data from after the primary endpoint.

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