**Clinical Study Protocol**

NCT Number: NCT05341115

Title: An Open label, Multicenter, Single-arm and Prospective Study to Assess the Efficacy and Safety of Leuprorelin 3M in the Treatment of central precocious puberty (CPP)

Study Number: Leuprorelin-4002

Document Version and Date: Amendment V.3.0, 30 May 2022

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

**TAKEDA PHARMACEUTICALS**

**PROTOCOL**

# An Open label, Multicenter, Single-arm and Prospective Study to Assess the Efficacy and Safety of Leuprorelin 3M in the Treatment of CPP



| | | | |
|---|---|---|---|
| **Sponsor:** | Takeda (China) International Trading Co., Ltd.<br><br>*37F，New Bund Center,NO.555 West Haiyang Rd, Pudong New Area, Shanghai , China， 200124* | | |
| **Study Number:** | Leuprorelin-4002 | | |
| **IND Number:** | NA | **EudraCT Number:** | NA |
| **Compound:** | Leuprorelin acetate depot 11.25mg 3M | | |
| **Date:** | 30th May, 2022 | **Version/Amendment Number:** | V.3.0 |

## Amendment History

| Date | Amendment Number | Amendment |
|---|---|---|
| Feb 14th 2022 | Protocol V.1.1 | Sponsor name and address clarification |
| Mar 24th 2022 | Protocol V.1.2 | The signature of the responsible Takeda medical officer. LH and FSH testing at screening visit and V2, V3, V4 |
| Apr 29 2022 | Protocol V2.0 | Version number |
| May 17, 2022 | Protocol V2.1 | SUSAR was added in section 10.1.4. ADR related contents were added in section 10.2.2 and 10.3. |

| | | |
|---|---|---|
| May 30, 2022 | Protocolc v3.0 | Version number and date updated |



# 1. Administrative information

## 1.1. Contacts



| Contact Type/Role | Contactor |
|---|---|
| Pharmacovigilance Monitor | [redacted] |
| Medical Monitor(medical advice on protocol and compound) | [redacted] Medical Advisor [redacted] |
| Responsible Medical Officer (carries overall responsibility for the conduct of the study) | [redacted] Medical Affairs, [redacted] |
| [redacted] clinical management advice on the conduct of the study) | [redacted] |

## 1.2. Approval

**REPRESENTATIVES OF TAKEDA**

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation E6(R2) Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.



**SIGNATURES**

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

| By signing this document, I am indicating that require no additional changes and approve this study protocal for the above study as it pertains to my area of expertise.<br>**Note**: An approver may delegate the review and approval of this document to an appropriately qualified and clearly identified (by name and title) designee. | | |
|---|---|---|
| **Print name and title of approver or designee** | **Signature of approver or designee** | **Date DD-MMM-YYYY** |
| [redacted] | | |
| [redacted]<br>**Local Medical Affairs Trial Clincian** | | |
| [redacted] | | |

## INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, prescribing information and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, life, dignity, integrity, confidentiality of personal information, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation, E6(R2) Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting adverse drug reactions (ADRs) and serious adverse events (SAEs) defined in Section 10.2 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the Investigator.



Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

TABLE OF CONTENTS

**LIST OF FIGURES AND TABLES**

## 2. STUDY SUMMARY

<table>
<tr><td colspan="2">Name of Sponsor(s):<br>Takeda China</td><td colspan="2">Compound:<br>Leuprorelin acetate depot 3M (11.25mg)</td></tr>
<tr><td colspan="2">Title of Protocol:<br>An Open label, Multicenter, Single-arm and Prospective Study to Assess the Efficacy and Safety of Leuprorelin 3M in the Treatment of central precocious puberty (CPP).</td><td>IND No.:NA</td><td>EudraCT No.:NA</td></tr>
<tr><td colspan="2">Study Number: Leuprorelin-4002</td><td colspan="2">Phase: IV</td></tr>
<tr><td colspan="4">Study Design:<br>This is an open-label, multicenter, single-arm and prospective study, to investigate the efficacy and safety of leuprolide acetate depot 11.25mg 3M formulations for the treatment of CPP in children in China. Approximately 80 subjects will be enrolled. The study includes a screening period (up to 2 weeks), a 6-month treatment period(24 weeks), and a post-treatment follow-up period (12 weeks) .</td></tr>
<tr><td colspan="4">Primary Objectives:<br>To evaluate the efficacy of leuprorelin acetate depot 11.25mg 3M in subjects with CPP.</td></tr>
<tr><td colspan="4">Secondary Objectives:<br>To evaluate the safety and efficacy of leuprorelin acetate depot 11.25mg 3M in subjects with CPP.</td></tr>
<tr><td colspan="4">Subject Population:<br>Subjects with appearance of secondary sexual characteristics before 8.0 years in girls and before 9.0 years in boys, with confirmed diagnosis of CPP.</td></tr>
</table>

| | |
|---|---|
| **Number of Subjects:**<br>Considering the drop-out rate 10% - 15%, a total number of 80 subjects are planned to be enrolled. | **Number of Sites:**<br>Approximately 5 sites in China |
| **Dose Level(s):**<br>CPP subjects with body weight ⩾20 kg will receive the recommended dose of leuprorelin acetate depot 11.25 mg subcutaneous administration (SC) every 12 weeks based on the standard of 30～180ug/kg/4w. It is not recommended to exceed 180 μg/kg. | **Route of Administration:**<br>Subcutaneous injection |
| **Duration of Treatment:**<br>24 weeks | **Period of Evaluation:**<br>2 weeks Screening Period<br>6-month Treatment Period<br>12 weeks Safety Follow-up Period |

- Main Criteria for Inclusion:
- In the opinion of the investigator, the subject and/or parent(s) or legal guardian are capable of understanding and complying with protocol requirements.
- The subject or the subject's parent(s) or legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
- Early appearance of secondary sexual characteristics: Girls ⩽8 years, Boys⩽9years.
- Body weight ⩾20 kg.
- According to the National Consensus Statement in China (2015), CPP is diagnosed when secondary sexual characteristics appeared before the age of 8 years in girls and 9 years in boys, a peak LH level > 5.0 IU/L with LH/FSH > 0.6 in stimulating test; evidence of gonadal development by ultrasonography (multiple ovarian follicles ⩾ 4 mm in any ovary or uterine enlargement in females or testicular volume ⩾ 4 mL in males); advanced BA ⩾ 1 year; linear growth acceleration with higer GV than normal children. BA is determined by Greulich and Pyle standards or Tanner-Whitehouse 3 (TW3) standards at screening.
- A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agrees to use adequate contraception* from signing of informed consent throughout the duration of the study and for 90 days after last dose.
- A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use routinely adequate contraception* from signing of informed consent throughout the duration of the study and for 90 days after last dose of study medication.

  *Definitions and acceptable methods of contraception are defined in Section 9.1.15 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.16 Pregnancy.
- The female subject who, at the discretion of the investigator, is deemed to be of child bearing potential must provide negative urine pregnancy test prior to receiving any dose of study medication drug administration and negative serum hCG pregnancy test at Screening.

- **Main Criteria for Exclusion:**
- The subject has received any investigational compound within 30 days prior to Screening.
- The subject has received GnRHa treatment in a previous clinical study or as a therapeutic agent.
- The subject is an immediate family member, study site employee, or is in a dependant relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
- The subject has any findings in his/her medical history, physical examination, or safety clinical laboratory tests giving reasonable suspicion of underlying disease that might interfere with the conduct of the trial.
- The subject has any concomitant medical condition that, in the opinion of the investigator, may expose a subject to an unacceptable level of safety risk or that affects subject compliance.
- The subject has any screening abnormal laboratory value that suggests a clinically significant underlying disease or condition that may prevent the subject from entering the study; or the subject has: creatinine ⩾1.5 mg/dL, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >2 times the upper limit of normal (ULN), or total bilirubin >2.0 mg/dL, with AST/ALT elevated above the limits of normal values.
- The subject has a history or clinical manifestations of significant adrenal or thyroid diseases or intracranial tumor or has a history of malignant disease.
- The subject has a history of hypersensitivity or allergies to leuprorelin, or related compounds including any excipients of the compound.
- The subject has a diagnosis of peripheral precocious puberty.
- The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to the Screening Visit.
- Subject or parent(s), at the discretion of the investigator, is unlikely to comply with the protocol or is unsuitable for any of other reason.
- If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 1 month after participating in this study; or intending to donate ova during such time period.
- If male, the subject intends to donate sperm during the course of this study or for 90 days thereafter.

**Main Criteria for Evaluation and Analyses:**

Primary endpoint: the percentage of subjects with peak LH suppression in GnRH stimulation (defined as LH peak value in GnRH stimualation ⩽ 3.0 IU/L) at Week 24.

Secondary endpoints: the percentage of subjects with Tanner stage regression or no progression at Week 24 compared with Baseline; basal LH and FSH level of subjects at Baseline, Week 24, Week 36; the percentage of subjects with decreased ratio of bone age over chronological age at Week 24 compared with Baseline; the percentage of subjects with decrease in first morning voided (FMV) urinary Gn at Week 24 compared with Baseline; incidence of treatment-emergent adverse events (TEAEs).

**Statistical Considerations:**

Descriptive statistics are used for summarizing the primary endpoints and secondary endpoints.

This study will be subject to interim analysis at an appropriate time.

**Sample Size Justification:**

The calculated sample size of 70, 58, 44 and 29 was based on the assumption that the proportion of peak LH suppression with GnRH stimulation is 80%, 85%, 90% and 95% respectively and a two-sided 95% confidence interval (CI) with a precision width of 0.2. Since the actual proportion of peak LH suppression with GnRH stimulation in Chinese remains unknown, a conservative sample size of 70 was determined.Considering the drop-out rate 10% - 15%, a total number of 80 subjects are planned to be enrolled. This study encourages sites to enroll subjects competitively, and each site enrolls at least 15 ~ 20 subjects. Within each site, eligible subjects will be enrolled until the site's subject quota has been reached.

# 3. STUDY REFERENCE INFORMATION

## 3.1. Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the clinical supplier list in the study manual. The identified vendors will perform these activities either in full or in partnership with the sponsor.

The study is being funded by Takeda. Payments for the conduct of the study that will be made to study sites (and, if applicable, investigators and/or other study staff) will be specified in the Clinical Study Site Agreement(s). All investigators and sub-investigators must declare potential conflicts of interests to the sponsor. The sponsor will provide a financial disclosure form that must be signed by each investigator and sub-investigator before the study starts at their study site; in addition, any potential conflicts of interests that are not covered by this financial disclosure form should be disclosed separately to the sponsor before the start of the study at their site.

All institutional affiliations of the investigator and sub-investigator should be declared on their curriculum vitae, which must be provided to sponsor before the start of the study.



## 3.2. Principal Investigator/Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study drug, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The signatory coordinating investigator will be required to review and sign the clinical study report (CSR) and by doing so agrees that it accurately describes the results of the study.

## 3.3. List of Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| CPP | Central precocious puberty |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| DL | Depot preparations of leuprolide acetate |

| | |
|---|---|
| E2 | Estradiol |
| FSH | Follicle stimulating hormone |
| GnRH | Gonadotropin-releasing hormone |
| GV | Growth Velocity |
| HTSDS | Height standard deviation score |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IRB/EC | Institutional Review Board/Ethics Committee |
| LC-MS/MS | Liquid chromatography/tandem mass spectrometry |
| LH | Luteinizing hormone |
| MAH | Marketing Authorization Holder |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PAH | Predicted adult height |
| PASS | Post-authorisation safety study |
| PMC | Post Marketing Commitments |
| PMS | Post-marketing Surveillance |
| PQI | Product Quality Issue |
| PRO | Patient-Reported Outcome |
| PTE | Pre-Treatment Event |
| PVA | Pharmacovigilance Agreement |
| SAE | Serious Adverse Event |
| SOC | System Organ Class |
| SSR | Special Situation Report |

# 4. INTRODUCTION

## 4.1. Background

Central precocious puberty (CPP) refers to the development of gonadotropin dependent onset of puberty before the age of 8 years in girls and 9 years in boys [1]. CPP is caused by the premature reactivation of the hypothalamic-pituitary-gonadal-axis[1]. Gonadotropin stimulation of the gonads induces the increase in sex steroid secretion that is responsible for the premature onset of somatic sexual characteristics and is associated with growth spurt and accelerated skeletal maturation that compromises adult height.

The GnRH analogs represent the treatment of choice for CPP[2]. These drugs suppress gonadotropin secretion through a desensitization and downregulation of GnRH receptors, leading to reduction of gonadal steroids to prepubertal levels [3].

The registration certificate of leuprorelin acetate depot 11.25mg 3M formulations will expire in March 2025. Takeda plans to submit PAC separately through supplementary application before submitting the registration application. Submit a Chinese CSR or interim analysis report that meets the registration application of submission requirements. The submission time is expected to be from February to May 2024.



## 4.2. Rationale for the Proposed Study

The monthly depot formulations of GnRH analogs are the main formulations used in the medical treatment of CPP[1, 2]. It has been demonstrated that they provide a steady release of drug [3] and improve significantly the short as well as the long-term outcome of children affected by CPP without relevant short-term or long-term side effects [1, 2, 4]. Three months depot formulations of GnRH agonists are now available, but there is limited data on quarterly 11.25 mg GnRH analog treatment in CPP in China.

Since CPP may require several years of treatment [2], the use of three-month formulations would increase the effectiveness and the compliance with the therapy, but data on the use of quarterly GnRH analogs in CPP remain scarce [6–10]. This study will assess the efficacy and safety of leuprolide acetate depot 11.25mg 3M formulations for the treatment of CPP in children in China. According to the requirements of Chinese CDE, it is necessary to conduct post marketing effectiveness and safety research.

## 4.3. Benefit/Risk Profile

The efficacy and safety of leuprorelin 11.25 mg 3 month depot formulation for CPP have been evaluated in global studies LEUb/CPP3M14/TIF; TAP/III/96/023; L-CP07-167; L-CP07-177. The data presented support the use of leuprorelin in this indication and was approved in China on 30th July, 2021 by center for drug evaluation (CDE). There is no expected difference in the efficacy and safety profile of leuprorelin 11.25 mg 3 month depot in Chinese subjects compared to the subjects included in the global studies. Therefore, leuprorelin is expected to show similar effects on gondadotropin suppression in this study and to contribute to the appropriate management of CPP in Chinese subjects.

With respect to safety, the following risks in the relevant population are identified in the current Chinese RMP:

- Injection site reaction (0.1~＜5%);
- Emotional instability (0.1~＜5%);
- Hypersensitivity (0.1~＜5%);
- Convulsions. (Ref: Risk Management Plan of Enantone® b1.0 based on Local Enantone®11.25 mg instruction )
- Slipped capital femoral epiphysis (CPP indication) is an Important Potential Risk and will be monitored via routine pharmacovigilance.( Ref: Risk Management Plan of Enantone® b1.0)

Based on the benefits that can be conferred to CPP subjects, as well as the risks and the appropriate measures to mitigate them, a favorable benefit-risk profile is expected for this population.



## 5. STUDY OBJECTIVES AND ENDPOINTS

### 5.1 Objectives

#### 5.1.1. Primary Objective(s)

To evaluate the efficacy of leuprorelin 11.25mg 3M in subjects with CPP.

#### 5.1.2. Secondary Objective(s)

To evaluate the safety and efficacy of leuprorelin 11.25mg 3M in subjects with CPP.

### 5.2. Estimands

Not Applicable

### 5.3. Endpoints

#### 5.3.1. Primary Endpoint(s)

The percentage of subjects with peak LH suppression in GnRH stimulation (defined as LH peak value in GnRH stimulation ≤ 3.0 IU/L) at Week 24.

#### 5.3.2. Secondary Endpoint(s)

The percentage of subjects with Tanner stage regression or no progression at Week 24 compared with Baseline; basal LH and FSH level of subjects at Baseline, Week 24, Week 36;
the percentage of subjects with decreased ratio of bone age over chronological age at Week 24 compared with Baseline; the percentage of subjects with decrease in first morning voided (FMV) urinary Gn at Week 24 compared with Baseline; incidence of treatment-emergent adverse events (TEAEs).

# 6. STUDY DESIGH AND DESCRIPTION

## 6.1. Study Design

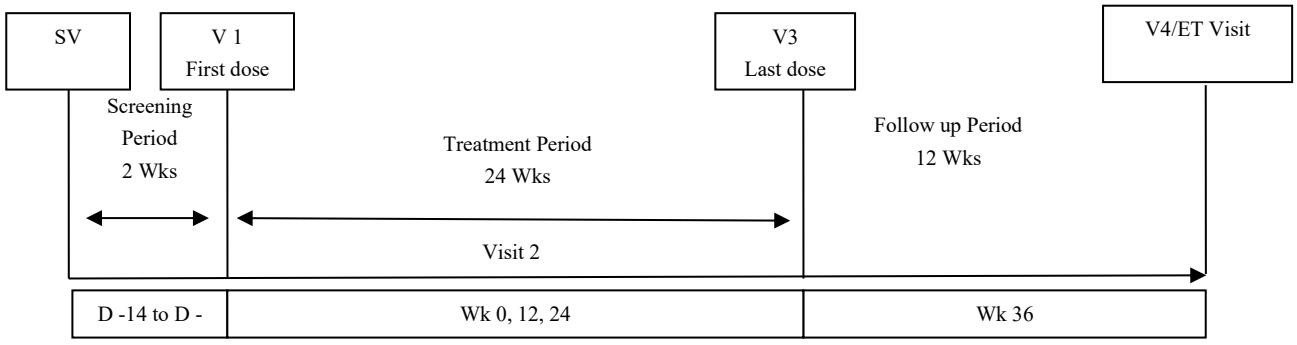
This is an open-label, multicenter, single-arm and prospective study, to investigate the efficacy and safety of Leuprorelin acetate depot 11.25mg 3M formulations for the treatment of CPP in children in China. Approximately 80 subjects will be enrolled. The study includes a screening period (up to 2 weeks), a 6-month treatment period (24 weeks), and a post-treatment follow-up period (12 weeks) .

CPP subjects with body weight ⩾20 kg will receive the recommended dose of leuprorelin acetate depot 11.25 mg subcutaneous administration (SC) every 12 weeks based on the standard of 30～180 μg/kg/4w. It is not recommended to exceed 180 μg/kg. The dose can be adjusted based on subject's condition and investigator's judgment. Pharmacokinetic studies in adults demonstrated that the quarterly formulation of 11.25 mg Leuprorelin is steadily released over 12 weeks period [3]. Each dose of the drug will be administered in outpatient hospital setting by appropriate site staff and the date of each administration will be registered on the clinical record of each child. Parents/ legal guardians of patients will be actively contacted some days before the injections to ensure them to follow the administration protocol.

The primary efficacy endpoint is the percentage of subjects with peak LH suppression in GnRH stimulation (defined as LH peak value in GnRH stimualation ⩽ 3.0 IU/L) at Week 24. Additional efficacy endpoints will include: the percentage of subjects with Tanner stage regression or no progression at Week 24 compared with Baseline; basal LH and FSH level of subjects at Baseline, Week 24, Week 36; the percentage of subjects with decreased ratio of bone age over chronological age at Week 24 compared with Baseline; the percentage of subjects with decrease in first morning voided (FMV) urinary Gn at Week 24 compared with Baseline.

Patients will be received an s.c. injection of study drug at V1,V2, V3. GnRHa stimulation will be repeated at screening visit and V2, V3 ( before every s.c. injection of study drug) or at early termination. Basal LH and FSH level testing (gonadotropins and sex steroids) will be repeated at screening visit and V2, V3,V4 ( before every s.c. injection of study drug) or at early termination. The stimulation test will use Gonadorelin uniformly, and the sponsor will coordinate the administration. Height and weight measurement will be performed at screening visit and V1, V2, V3, V4 (before every s.c. injection of study drug) or at early termination. Physical exams and pubertal staging will be performed at screening visit and V1, V2, V3, V4 (before every s.c. injection of study drug) or at early termination. and a repeat BA radiograph at V2, V3, V4 (before the s.c. injection of study drug) or at early termination. The first morning voided (FMV) urinary Gn will be detected at screening visit and V1,V2, V3, V4 ( before every s.c. injection of study drug) or at early termination. Adverse events will be collected and reported at each study visit or at early termination. Treatment-emergent adverse events will be coded using the Medical Dictionary for Regulatory Activities(MedDRA) dictionary.

**Figure 1** ***Schematic of Study Design***




V=visit, D=day, Wk=week, SV=Screening Visit, EOS= End of Study, ET=Early Termination.



**Table 1** ***Study Schedule***

| Procedures /Assessments | Screening Visit | V1 | V2 | V3 | V4 | Early Temination Visit |
|---|---|---|---|---|---|---|
| | | Week 0 | Week 12 | Week 24 | Week 36 | |
| **Study cycle (Days)** | **14 days** | **D0** | **D84** | **D168** | **D252** | |
| **Window period** | | | **± 3d** | **± 3d** | **± 3d** | |
| Informed Consent | X | | | | | |
| Inclusion Criteria/Exclusion Criteria | X | | | | | |
| Demographic data | X | | | | | |
| CEA, AFP, β-HCG | X | | | | | |
| Predicted adult height(a) | X | | | | | |
| Concurrent medical conditions | X | | | | | |
| Cranial MRI (b) | X | | | | | |
| Medication history | X | | | | | |
| Medical history | X | | | | | |

| Procedures /Assessments | Screening Visit | V1 | V2 | V3 | V4 | Early Temination Visit |
|---|---|---|---|---|---|---|
| | | Week 0 | Week 12 | Week 24 | Week 36 | |
| **Study cycle (Days)** | **14 days** | **D0** | **D84** | **D168** | **D252** | |
| **Window period** | | | **± 3d** | **± 3d** | **± 3d** | |
| Urine pregnancy test(c) | | X | | | | |
| Vital signs | X | X | X | X | X | X |
| Age (years) | X | X | X | X | X | X |
| Height (SDS) | X | X | X | X | X | X |
| Growth rate (cm/year) | X | X | X | X | X | X |
| Weight (kg) | X | X | X | X | X | X |
| BMI (SDS) | X | X | X | X | X | X |
| Bone age (years)(d)* | X | | X | X | X | X |
| BA/CA* | X | | X | X | X | X |
| Hematology, Urine analysis, Clinical Chemistry | X | | X | X | X | X |
| ECG | X | | X | X | X | X |
| Pregnancy avoidance counseling | X | X | X | X | X | X |
| Estradiol (pg/ml)/ Testosterone (ng/ml)* | X | X | X | X | X | X |
| Stimulation Test(e) | X | | X | X | | X |
| LH and FSH | X | | X | X | X | X |
| FMV urinary Gn* | X | X | X | X | X | X |
| Tanner Stage | X | X | X | X | X | X |
| Gonads ultrasonography(f) | X | X | X | X | X | X |

| Procedures /Assessments | Screening Visit | V1 | V2 | V3 | V4 | Early Temination Visit |
|---|---|---|---|---|---|---|
| | | Week 0 | Week 12 | Week 24 | Week 36 | |
| **Study cycle (Days)** | **14 days** | **D0** | **D84** | **D168** | **D252** | |
| **Window period** | | | **± 3d** | **± 3d** | **± 3d** | |
| Leuprorelin injection(g) | | X | X | X | | |
| PTE assessment | X | X | | | | |
| AE assessment | | X | X | X | X | X |
| Concomitant medication | X | X | X | X | X | X |

(a) Predicted adult height will be evaluated using Bayley-Pinneau method.

(b) Cranial MRI can consist of only pituitary scan, including saddle region.

(c) The female subject who, at the discretion of the investigator, is deemed to be of child bearing potential must provide negative urine pregnancy test at Day –1 or Day 1 prior to drug administration.

(d) Bone age will be evaluated by investigators at each site using TW3 standards or Greulich-Pyle standards at Screening. All bone age x-ray will be sent for central reading before the end of the study.

(e) Stimulation test: Blood samples will be collected at 0, 30, and 60, 90 minutes after the injection of GnRH. It is acceptable to use both GnRH and GnRHa in stimulation test; however, it is preferable to use GnRH as priority. These results if available already can be used as part of screening. If stimulation test result is already available – whether at same site or hospital – within 28 days prior to first dose, the result can be used for screening, under the condition that the Site retains a copy of the data in file notes as source documents. The stimulation test will use Gonadorelin uniformly, and the sponsor will coordinate the administration.

(f) Pelvic ultrasonography will be performed for females to measure, uterus size and number/size of follicles. For males, ultrasonography will be performed to measure the testicular volume. These results if available already can be used as part of screening. If result is already available – whether at same site or hospital – within 28 days prior to first dose, the result can be used for screening, under the condition that the Site retains a copy of the data in file notes as source documents.

(g) Subcutaneous injection Leuprorelin every 12 weeks based on the standard of 30～180 μ g/kg/4w.

* These medical examination results need to be issued by the central laboratory.Blood hormones and urinary hormones will be sent to the central laboratory for testing. And all bone age x-ray will be sent for central reading.



## 6.2. Justification for Study Design, Dose, and Endpoints

The design proposed in this study is acceptable to investigate the efficacy and safety of Leuprorelin 11.25 mg 3M depot formulations for the treatment of CPP in children in China.

The dose of leuprorelin used in clinical practice varies in China. The label dose is 30～180 μg/kg body weight. The initial dose of 80-100 μg/kg body weight up to 3.75 mg was recommended in the treatment guideline issued by China Ministry of Health. It is also recommended to adjust the dose during the maintenance period depending on suppression of gonadal axis function. According to the instruction of 11.25 mg leuprorelin in China, the dose range is 30-180 μ g/kg/4w depending on suppression of gonadal axias function and weight changes, every 12

weeks for patients to be subcutaneously. The dose can be adjusted based on physician's judgment. The inclusion/exclusion criteria are in alignment with Chinese treatment guideline to ensure the treatment is given to the appropriate subjects.

The efficacy and safety measurements and the clinical and routine laboratory procedures used in this study are standard and generally accepted.

### 6.3. Premature Termination or Suspension of Study or Study Site

#### 6.3.1. Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the Leuprorelin 11.25 mg depot, such as the risk of the tolerance to the Leuprorelin 11.25 mg depot treatment is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.
- Study-specific criteria for terminating the study (eg, study meets predefined rule for futility or benefit).



#### 6.3.2. Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

#### 6.3.3. Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (IEC) or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

## 7. SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed before first dose or other.

### 7.1. Inclusion Criteria

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

1. In the opinion of the investigator, the subject and/or parent(s) or legal guardian are capable of understanding and complying with protocol requirements.

2. The subject or the subject's parent(s) or legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. Early appearance of secondary sexual characteristics: Girls ⩽8 years, Boys⩽9years
4. Body weight ⩾20 kg
5. According to the National Consensus Statement in China (2015), CPP is diagnosed when secondary sexual characteristics appeared before the age of 8 years in girls and 9 years in boys, a peak LH level > 5.0 IU/L with LH/FSH > 0.6 in stimulating test; evidence of gonadal development by ultrasonography (multiple ovarian follicles ⩾ 4 mm in any ovary or uterine enlargement in females or testicular volume ⩾ 4 mL in males); advanced BA ⩾ 1 year; linear growth acceleration with higer GV than normal children. BA is determined by Greulich and Pyle standards or Tanner-Whitehouse 3 (TW3) standards at screening.
6. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agrees to use adequate contraception* from signing of informed consent throughout the duration of the study and for 90 days after last dose.
7. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use routinely adequate contraception* from signing of informed consent throughout the duration of the study and for 90 days after last dose of study medication.

*Definitions and acceptable methods of contraception are defined in Section 9.1.15 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.16 Pregnancy.

8. The female subject who, at the discretion of the investigator, is deemed to be of child bearing potential must provide negative urine pregnancy test prior to receiving any dose of study medication drug administration and negative serum hCG pregnancy test at Screening.



### 7.2. Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has received any investigational compound within 30 days prior to Screening.
2. The subject has received GnRHa treatment in a previous clinical study or as a therapeutic agent.
3. The subject is an immediate family member, study site employee, or is in a dependant relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
4. The subject has any findings in his/her medical history, physical examination, or safety clinical laboratory tests giving reasonable suspicion of underlying disease that might interfere with the conduct of the trial.

5. The subject has any concomitant medical condition that, in the opinion of the investigator, may expose a subject to an unacceptable level of safety risk or that affects subject compliance.
6. The subject has any screening abnormal laboratory value that suggests a clinically significant underlying disease or condition that may prevent the subject from entering the study; or the subject has: creatinine ≥1.5 mg/dL, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >2 times the upper limit of normal (ULN), or total bilirubin >2.0 mg/dL, with AST/ALT elevated above the limits of normal values.
7. The subject has a history or clinical manifestations of significant adrenal or thyroid diseases or intracranial tumor OR has a history of malignant disease.
8. The subject has a history of hypersensitivity or allergies to leuprorelin, or related compounds including any excipients of the compound.
9. The subject has a diagnosis of peripheral precocious puberty.
10. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to the Screening Visit.
11. Subject or parent(s), at the discretion of the investigator, is unlikely to comply with the protocol or is unsuitable for any of other reason.
12. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 1 month after participating in this study; or intending to donate ova during such time period.
13. If male, the subject intends to donate sperm during the course of this study or for 90 days thereafter.



### 7.3. Excluded Medication, Procedures and Treatments

The subjects should follow physician's instruction on Medication, Procedures and Treatments. Any concomitant medications, procedures and treatments should be recorded.

Hormonal contraceptives should be avoided during the study. In addition, all growth hormones need to be avoided for this study.

### 7.4. Diet, Fluid, Activity Control

The subjects should follow physician's instruction on diet, fluid and activity.

## 7.5. Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section 9.1.14.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.

   - Liver function test (LFT) Abnormalities

     Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.8), if the following circumstances occur at any time during study medication treatment:

     – ALT or AST >8 × ULN, or

     – ALT or AST >5 × ULN and persists for more than 2 weeks, or

     – ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or clinical features of jaundice

     – ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

2. Significant protocol deviation. The discovery after the first dose of study medication that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE or lack of efficacy).

5. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
6. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.16.

7. Lack of efficacy. The investigator has determined that the subject is not benefiting from investigational treatment; and, continued participation would pose an unacceptable risk to the subject.
8. Other.

Note: The specific reasons should be recorded in the "specify" field of the eCRF.

### 7.6. Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

## 8. CLINICAL STUDY MATERIAL MANAGEMENT

### 8.1. Study Drug and Materials

#### 8.1.1. Dosage Form, Manufacturing, Packaging, and Labeling

Leuprorelin Acetate Microspheres For Injection 11.25mg

Made by Takeda

Each box contains 1 injection solvent，DPS

Specifications for prefilled syringes：1 box ( Prefilled syringe, the front chamber is sterile powder, the back chamber is 1ml solvent.)

*8.1.1.1. Study Drug*

Leuprorelin acetate depot 3M (11.25mg)



#### 8.1.2. Storage

Investigational drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Investigational drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

#### 8.1.3. Dose and Regimen

CPP subjects with body weight ≥20 kg will receive the recommended dose of leuprorelin acetate depot 11.25 mg subcutaneous administration (SC) every 12 weeks based on the standard of 30～180 μg/kg/4w. It is not recommended to exceed 180 μg/kg. The dose can be adjusted based on subject's condition and investigator's judgment.

#### 8.1.4. Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database.

Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE eCRF(s) according to Section 10.0, Pretreatment Events and Adverse Events.

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2, Collection and Reporting of SAEs.

In the event of drug overdose, the subject should be treated symptomatically.

## 8.2. Investigational drug Dispensing Procedures

The investigator or investigator's designee will inject the investigational drug to eligible subject at Visit 1. At subsequent visits, the investigator or designee will again inject investigational drug to the subject.

Subjects will receive treatment according to study schedule.

## 8.3. Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug (Leuprorelin 11.25 mg), the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment. If there are any discrepancies between the packing list versus the actual product received, the sponsor must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs (Leuprorelin 11.25 mg) received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date it is provided to the investigator or designee.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug accountability used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator or designee must record the current inventory of all sponsor-supplied drugs (Leuprorelin 11.25 mg), on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiry date and amount dispensed including initials of the person dispensing the drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

In the event of expiry date extension of sponsor-supplied drug already at the study site, sponsor-supplied drugs may be relabeled with the new expiry date at that site. In such cases, Takeda or its designee will prepare additional labels, certificates of analyses, and all necessary documentation for completion of the procedure at the sites.



## 9. STUDY PLAN

### 9.1. Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible.

#### 9.1.1. Informed Consent Procedure

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each subject at the time; this subject number will be used throughout the study.

Subjects/ legal guardians will be asked to consent via paper consent forms. The investigational site is responsible for the consenting process.

#### 9.1.2. Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include or age, sex, race as described by the subject, height, weight of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions .

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within one month prior to signing of informed consent.

### 9.1.3. Physical Examination Procedure

A baseline physical examination (defined as the assessment prior to first dose of study drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; (11) genitourinary system[GU should only be included if applicable to the indication under study]; and (12) other. All subsequent physical examinations should assess clinically significant changes from the assessment prior to first dose examination.



### 9.1.4. Weight, Height

A subject should have weight and height measured while wearing indoor clothing and with shoes off. Height is recorded in cm with 1 decimal place. Weight is collected in kg with 2 decimal places.

### 9.1.5. Vital Sign Procedure

Vital signs will include body temperature infra-axillary measurement, respiratory rate, sitting blood pressure (resting more than 5 minutes), and pulse (beat per minute [bpm]).

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained preferably within 0.5 hour before or after the scheduled blood draw. The most important consideration is for patient to be in a calm and stable state, when taking vital signs, as deemed suitable at the discretion of the investigator.

### 9.1.6. Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the (e)CRF.

### 9.1.7. Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, electrocardiogram (ECG), or physical examination abnormalities noted at screening examination.

### 9.1.8. Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 40 mL, and the approximate total volume of blood for the study is 200 mL.

**Clinical Laboratory Tests**

| Hematology | Clinical Chemistry | Urinalysis |
|---|---|---|
| RBC<br>WBC<br>Hemoglobin<br>Hematocrit<br>Platelets | ALT<br>Albumin<br>Alkaline phosphatase<br>AST<br>Total bilirubin<br>Total protein<br>Creatinine<br>Blood urea nitrogen<br>Creatine kinase<br>GGT<br>Potassium<br>Sodium<br>Glucose<br>Chloride<br>Bicarbonate<br>Calcium<br>Magnesium | pH<br>Specific gravity<br>Protein<br>Glucose<br>Blood<br>Nitrite<br><br>Microscopic Analysis (only if positive dipstick results):<br>RBC/high power field<br>WBC/high power field<br>Epithelial cells, casts etc |
| **Other:**<br>GnRH stimulation test<br>LH and FSH<br>Estradiol or testosterone<br>Serum bone metabolism biomarkers- phosphorus, 25-hydroxy vitamin D, osteocalcin, crosslaps | | |

| Other Screening/Safety | Urine |
|---|---|
| AFP, CEA, β-HCG | Urine pregnancy test * |

AFP= alpha-fetoprotein, β-HCG= beta human chorionic gonadotropin, CEA=carcino-embryonic antigen, GGT= glutamyl transferase, RBC=red blood cells, WBC=white blood cells.

*The female subject who, at the discretion of the investigator, is deemed to be of child bearing potential must provide negative urine pregnancy test at Day –1 or Day 1 prior to drug administration.

The local laboratory will perform laboratory tests for hematology, serum chemistries, urinalysis, estradiol, testosterone, bone metabolism markers, LH, FSH, AFP, CEA, and β-HCG . The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was noted.

If the ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study medication, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section **错误!未找到引用源。**2.3 Reporting of Abnormal Liver Function Tests for reporting requirements).

The investigator or designee is responsible for transcribing or attaching laboratory results to the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.



### 9.1.9. ECG Procedure

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the investigational site) will interpret the ECG within normal limits, abnormal but not clinically significant, or abnormal and clinically significant.

### 9.1.10. Bone Age

Bone age will be evaluated by investigators at each site using TW3 standards or Greulich-Pyle standards, and the result will be recorded in the eCRF. All BA x-ray will be sent for central reading before the end of the study. If BA x-ray result is already available – whether in the same hospital or other hospital - within 28 days prior to first dose, the result be used for screening, under the condition that the Site retain a copy of the data/image in file notes as source documents.

### 9.1.11. Tanner Stage

Tanner divided the development of reproductive system into 5 stages according to the characteristics of puberty sexual development for clinical evaluation[13]. The progression was defined that either breast/genitals or pubic hair score had increased score compared with baseline score. Otherwise the status was classified as regression or no progression.

| Stage | Breast | Testis, Penis | Pubic Hair |
|---|---|---|---|
| 1 | Infantile type | Infantile type, testicular diameter＜2.5cm | None |
| 2 | Induration, nipple and areola slightly increased | Bilateral testis and scrotum enlarged; testicular diameter ＞2.5 cm (4-8 ml); scrotal skin becomes red, thin and wrinkled; the penis is slightly enlarged. | A few sparse straight hair, light color. Girls are limited to labia; in boys, it's limited to the base of the penis. |
| 3 | The breast and areola are larger, and the side is semicircular. | The scrotum and bilateral testis are enlarged, and the length of testis is about 3.5cm (10-15ml); the penis began to grow. | The hair becomes dark and thick, which is seen on the pubic symphysis. |
| 4 | Areola, nipple enlargement, lateral view of the protrusion in the semicircular breast. | The color of scrotal skin becomes darker; the penis grows and thickens, and the glans develops; the length of testis is about 4cm (15-20ml). | As adults, but the distribution area is small. |
| 5 | Adult type | Adult type, testicular length > 4cm (＞20ml). | Adult type |



### 9.1.12. Cranial MRI

Cranial magnetic resonance imaging MRI will be performed at Screening Visit only. Investigators will assess the presence of any intracranial tumor. The results will be recorded in the eCRF. If Cranial MRI result is already available – whether in the same hospital or other hospital - within 28 days prior to first dose, the result can be used for screening, under the condition that the Site retain a copy of the data/image in file notes as source documents. Cranial MRI can consist of only pituitary scan, including saddle region.

### 9.1.13. Gonads Ultrasonography

Pelvic ultrasonography will be performed for females to measure ovarian volume, uterus size and volume and number of follicles. For males, ultrasonography will be performed to measure the testicular volume. The results will be recorded in the eCRF.

### 9.1.14. Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject is found to be not eligible at this visit, the investigator should complete the eCRF.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal.
- Study termination.
- Other.

Subject numbers assigned to subjects who fail screening should not be reused.

### 9.1.15. Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 90 days after last dose of study medication, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period.

From signing of informed consent, throughout the duration of the study, and for 90 days after last dose of study medication, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition they must be advised not to donate ova during this period.



*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (eg, defined as at least 1 year since last regular menses with an FSH >40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented).

**Sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, where medications and devices containing hormones are excluded, the only acceptable methods of contraception are:

| **Barrier methods (each time the subject has intercourse):** | **Intrauterine devices (IUDs):** |
|---|---|
| Male condom PLUS spermicide. | Copper T PLUS condom or spermicide. |
| Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide. | #Progesterone T PLUS condom or |

| | |
|---|---|
| Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide. | spermicide. |

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.

During the course of the study, regular serum/urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures (Study Schedule). In addition to a negative serum hCG pregnancy test at Screening, subjects also must have a negative urine hCG pregnancy at test Day –1 or Day 1 prior to receiving any dose of study medication drug administration.

### 9.1.16. Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug Leuprorelin should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 90 days after the last dose, should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study medication, eg, after within 30 days of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received.

All pregnancies in subjects on active study drug including comparator will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

## 9.2. Monitoring Subject Treatment Compliance

Subjects will be injected the study medication Leuprorelin 11.25 mg on site by investigator or investigator's designee.

If a subject is persistently noncompliant, defined as missing two consecutively scheduled drug injections against what is stipulated in the protocol's schedule of study procedures, with the study medication Leuprorelin 11.25 mg, it may be appropriate to withdraw the subject from the study. All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

## 9.3. Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Study Schedule. Assessments should be completed at the designated visit.

### 9.3.1. Screening Visit

Subjects will be screened within 14 days prior to first dose (Week 0, Visit 1). Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.

Procedures to be completed at Screening (Visit 1) include:

- Informed consent
- Inclusion/exclusion criteria
- Demographics, medical history, and medication history
- Physical examination
- Vital signs
- Growth rate
- Weight, height, BMI
- Concomitant medications
- Concurrent medical conditions
- Predicted adult height
- Estradiol or Testosterone
- Tanner staging evaluation
- Bone age, BA/CA
- Hematology, Urine analysis, Clinical Chemistry
- Pregnancy avoidance counseling, for female subject who, at the discretion of the investigator, is deemed to be of childbearing potential or , the male subject who is nonsterilized and sexually active with a female partner of childbearing potential
- ECG
- Gonads ultrasonography
- FMV urinary Gn
- Stimulation test
- LH and FSH

- Cranial MRI
- CEA, AFP, β-HCG
- PTE assessment
- Assign subject number

### 9.3.2. Study Entrance - Visit 1 (Week 0, first dose)

Study entrance will take place on Day 0 (Visit 1). The following procedures will be performed and documented during Study Entrance:

- Vital signs
- Growth rate
- Weight, height, BMI
- Urine pregnancy test
- Concomitant medications
- Tanner staging evaluation
- Gonads ultrasonography
- Pregnancy avoidance counseling, for female subject who, at the discretion of the investigator, is deemed to be of childbearing potential or , the male subject who is nonsterilized and sexually active with a female partner of childbearing potential
- Estradiol or Testosterone
- FMV urinary Gn
- Injection of Investigational Drug by investigator or investigator's designee
- PTE assessment
- AE assessment



If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for study entrance, the subject should be assigned a subject number. Subjects will be instructed on when to take the first dose of investigational drug as described in Section 6.1.

### 9.3.3. Treatment Phase - Visit 2 (Week 12)

Visit 2 will take place on Week 12. The following procedures will be performed and documented during this visit:

- Vital signs
- Growth rate
- Weight, height

- Concomitant medications
- Tanner staging evaluation
- Gonads ultrasonography
- Bone age, BA/CA
- Hematology, Urine analysis, Clinical Chemistry
- Pregnancy avoidance counseling, for female subject who, at the discretion of the investigator, is deemed to be of childbearing potential or , the male subject who is nonsterilized and sexually active with a female partner of childbearing potential
- ECG
- Estradiol or Testosterone
- FMV urinary Gn
- Stimulation test
- LH and FSH
- Injection of Investigational Drug by investigator or investigator's designee
- AE assessment

### 9.3.4. Treatment Phase - Visit 3 (Week 24)

Visit 3 will take place on Week 24. The following procedures will be performed and documented during this visit:



- Vital signs
- Growth rate
- Weight, height, BMI
- Concomitant medications
- Tanner staging evaluation
- Gonads ultrasonography
- Bone age, BA/CA
- Hematology, Urine analysis, Clinical Chemistry
- Pregnancy avoidance counseling, for female subject who, at the discretion of the investigator, is deemed to be of childbearing potential or , the male subject who is nonsterilized and sexually active with a female partner of childbearing potential.
- ECG

- Estradiol or Testosterone
- FMV urinary Gn
- Stimulation test
- LH and FSH
- Injection of Investigational Drug by investigator or investigator's designee
- AE assessment

### 9.3.5. Follow-up -- Visit 4 (Week 36)

Follow-up Visit will take place on Week 36. The following procedures will be performed and documented during this visit:

- Vital signs
- Growth rate
- Weight, height, BMI
- Concomitant medications
- Tanner staging evaluation
- Gonads ultrasonography
- Estradiol or Testosterone
- Bone age, BA/CA
- Hematology, Urine analysis, Clinical Chemistry
- Pregnancy avoidance counseling, for female subject who, at the discretion of the investigator, is deemed to be of childbearing potential or , the male subject who is nonsterilized and sexually active with a female partner of childbearing potential.
- ECG
- FMV urinary Gn
- LH and FSH
- AE assessment



### 9.3.6. Early Temination Visit

Early temination Visit will take place on when a patient chooses to quit the study ahead of time. The following procedures will be performed and documented during this visit:

- Vital signs
- Growth rate

- Weight, height, BMI
- Concomitant medications
- Tanner staging evaluation
- Estradiol or testosterone
- FMV urinary Gn
- Bone age, BA/CA
- Hematology, Urine analysis, Clinical Chemistry
- Pregnancy avoidance counseling, for female subject who, at the discretion of the investigator, is deemed to be of childbearing potential or , the male subject who is nonsterilized and sexually active with a female partner of childbearing potential.
- ECG
- Gonads ultrasonography
- Stimulation test
- LH and FSH
- AE assessment

For all subjects receiving study medication, the investigator must complete the End of Study CRF page.



## 10. PRETREATMENT EVENTS AND ADVERS EVENTS

### 10.1. Definitions

#### 10.1.1. PTEs

A pretreatment event is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but before administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

#### 10.1.2. AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug. This includes any newly occurring event or a previous condition that has increased in severity or frequency since the administration of study drug.

### 10.1.3. Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- Diagnoses vs signs and symptoms:
- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are only considered to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG re-test and/or continued monitoring of an abnormal value or finding are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as AEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the event term recorded captures the change in the condition (eg, “worsening of…”).
- If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as an AE if the condition becomes more frequent, serious or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from baseline (eg “worsening of…”).

- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as an AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in intensity of AEs:

- If the subject experiences changes in intensity of an AE, the event should be captured once with the maximum intensity recorded.

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.



Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered AEs, but instead will be documented on an (e)CRF. Any manifested side effects will be considered AEs and will be recorded on the AE page of the (e)CRF.

### 10.1.4. SAEs and SUSAR

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.

2. Is LIFE THREATENING.

- The term “life threatening” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.

4. Results in persistent or significant DISABILITY/INCAPACITY.

5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.

6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:

- May require intervention to prevent items 1 through 5 above.
- May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

Suspected Unexpected Serious Adverse Reaction(SUSAR) is defined as any suspected adverse reaction to investigational product that is both serious and unexpected (“unexpected” means an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information).



### 10.1.5. AEs of Special Interest

An AE of Special Interest (serious or non-serious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda.

### 10.1.6. Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows: :

| | |
|---|---|
| Mild: | The event is transient and easily tolerated by the subject. |
| Moderate: | The event causes the subject discomfort and interrupts the subject’s usual activities. |
| Severe: | The event causes considerable interference with the subject’s usual activities. |

### 10.1.7. Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

| | |
|---|---|
| Related: | An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible. |

| | |
|---|---|
| Not Related: | An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments. |

### 10.1.8. Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

### 10.1.9. Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or physician.

### 10.1.10. Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.



### 10.1.11. Frequency

Episodic AEs/PTE (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

### 10.1.12. Action Concerning Study Medication

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study medication was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE.
- Dose Reduced – the dose was reduced due to the particular AE.
- Dose Increased – the dose was increased due to the particular AE.
- Dose Interrupted – the dose was interrupted due to the particular AE.

### 10.1.13. Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/PTE.
- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has

not returned to the normal range or to baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving".

- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.
- Fatal – the AEs/PTEs which are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

## 10.2. Procedures

### 10.2.1. Collection and Reporting of AEs

*10.2.1.1.PTE and AE Collection Period*

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication (Visit 1) or until screen failure

Collection of AEs will commence from the time that the subject is first administered study medication (Visit 1). Routine collection of AEs will continue until Visit 4 or premature termination Visit.



*10.2.1.2.PTE and AE Reporting*

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the CRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date
3. Severity.
4. Investigator's opinion of the causal relationship between the event and administration of study medication(s) (related or not related) (not completed for PTEs).
5. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
6. Action concerning study medication (not applicable for PTEs).
7. Outcome of event.
8. Seriousness.

### 10.2.2. Collection and Reporting of ADRs/SAEs

All AEs spontaneously reported by the subject or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the (e)CRF (see Section 10.2.1 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as a single comprehensive event.

ADRs/SAEs must be reported (see Section 10.2.1 for the period of observation) by the investigator to the Takeda Global Patient Safety Evaluation department or designee within 24 hours of becoming aware of the event. This will be done by transmitting an electronic data capture (EDC) report. If transmission of an EDC report is not feasible within 24 hours of becoming aware of the event, then a facsimile (fax) of the completed Takeda paper-based form should be submitted to the fax number below. A sample of the paper-based form and processing directions are in the Study Manual.



| **ADR/SAE Reporting Contact Information** | |
|---|---|
| **Fax numbers:** | **Rest of World(outside US and Canada)**<br>+1-224-554-1052 |
| **Email address:** | eupv@tgrd.com |

In case of fax, site personnel need to confirm successful transmission of all pages and include an email address on the cover sheet so that an acknowledgment of receipt can be returned via email within 1 business day.

Email submission of forms with a PDF attachment should only be used in the case where fax is not possible and EDC is not feasible within 24 hours of receiving the event. In case of email, site

personnel need to confirm successful transmission by awaiting an acknowledgment of the receipt via email within 1 business day.

If ADRs/SAEs are reported via fax or by email, EDC must be updated as soon as possible with the appropriate information. Information in the report or form must be consistent with the data provided on the eCRF.

An ADR/SAE should be reported by the investigator within 24 hours/1 business day of the ADR/SAE occurrence, along with any relevant information. The investigator should submit the detailed Form to within 10 calendar days. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study drug(s).
- Causality assessment.

The form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1.



Any ADR/SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

### 10.2.3. Reporting of Abnormal Liver-Associated Test Results

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases CRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.8 must also be performed. In addition, an LFT Increases CRF must be completed and transmitted with the Takeda SAE form

## 10.3. Follow-up of ADRs/SAEs

If information not available at the time of the first report becomes available at a later date, the investigator will transmit a follow-up EDC report (or a paper-based form in an EDC report is not feasible) (copy [For local studies in Japan]) or provide other written documentation and transmit it immediately .Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All ADRs/SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

### 10.3.1. Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable ADRs/SAEs which are occurred in this study to regulatory authorities, investigators and IECs as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IEC in accordance with national regulations.



## 11. STUDY-SPECIFIC COMMITTEES

No steering committee, data monitoring committee or clinical endpoint committee will be used in this study.

## 12. DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary (WHODRUG).

### 12.1. Electronic CRFs

Completed (e)CRFs are required for each subject.

CRO will supply study sites with access to eCRFs. CRO will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. (e)CRFs must be completed in China.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by CRO and will be answered by the site.

The principal investigator must review the (e)CRFs for completeness and accuracy and must the appropriate (e)CRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the (e)CRFs.

After submission of the CRFs to the sponsor, any change of, modification of or addition to the data on CRFs should be made by the investigator with use of change and modification records of CRFs (Data Clarification Form) provided by CRO. The principal investigator must review the Data Clarification Form for completeness and accuracy, and must sign, or sign and seal, and date the form.

After the lock of the study database, any change of, modification of or addition to the data on the (e)CRFs should be made by the investigator with use of change and modification records. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

(e)CRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the (e)CRFs. The completed (e)CRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.



### 12.2. Record Retention

The investigator agrees to keep the records stipulated in Section 11 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, ICH E6(R2) Section 5.5.11 requires the investigator to retain essential documents specified in ICH E6(R2) (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6(R2) Section 5.5.11 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

## 13. STATISTICAL METHODS

### 13.1. Data Source / Data Collection

GnRHa stimulation and basal LH and FSH level testing (gonadotropins and sex steroids) will be

repeated at screening visit and V2, V3 (D84, D168, before every s.c. injection of study drug) or at premature termination. Height and weight measurement will be performed at screening visit and V1, V2, V3, V4 (D0, D84, D168, D252, before every im injection of study drug) or at premature termination. Physical exams and pubertal staging will be performed at screening visit and V1, V2, V3, V4 (D0, D84, D168, D252, before every s.c. injection of study drug) or at premature termination. and a repeat BA radiograph at D84, D168 and D252 (before the s.c. injection of study drug) or at premature termination. The first morning voided (FMV) urinary Gn will be detected at screening visit and V1,V2, V3, V4 (D0, D84, D168, D252, before every s.c. injection of study drug) or at premature termination. Adverse events will be collected and reported at each study visit (D0, D84, D168, D252) or at premature termination.

### 13.2. Data Collection Procedures

The hypothalamic-pituitary-gonadal axis was investigated by measuring plasma LH and FSH peak concentrations under GnRH stimulation. Basal serum samples were obtained prior to GnRH injection. Poststimulation samples for measurement of LH and FSH levels were acquired 30, 45, 60, and 90 minutes after injection. Serum LH , FSH and estradiol levels were measured by immunoradiometric assay with analytical sensitivity and respectively.



### 13.3. Variables (Exposures, Outcomes and/or Endpoints and Other Study Variables)

- Peak LH suppression in GnRH stimulation (defined as LH peak value in GnRH stimualation ≤ 3.0 IU/L) at Week 24;
- Tanner stage regression or no progression at Week 24 compared with Baseline;
- Basal LH and FSH level of subjects at Baseline, Week 24, Week 36;
- Decreased ratio of bone age over chronological age at Week 24 compared with Baseline;
- Decrease in first morning voided (FMV) urinary Gn at Week 24 compared with Baseline;
- Incidence of treatment-emergent adverse events (TEAEs).

### 13.4. Determination of Sample Size

The calculated sample size of 70, 58, 44 and 29 was based on the assumption that the proportion of peak LH suppression with GnRH stimulation is 80%, 85%, 90% and 95% respectively and a two-sided 95% confidence interval (CI) with a precision width of 0.2. Since the actual proportion of peak LH suppression with GnRH stimulation in Chinese remains unknown, a conservative sample size of 70 was determined. Considering the drop-out rate 10% - 15%, a total number of 80 subjects are planned to be enrolled. This study encourages sites to enroll subjects competitively, and each site enrolls at least 15 ~ 20 subjects. Within each site, eligible subjects will be enrolled until the site’s subject quota has been reached.

### 13.5. Analysis population

- Enrolled population: All the eligible patients enrolled in this study.

- Safety population: All included patients who have been under treatment with Leuprorelin or who are first prescribed Leuprorelin, receive at least one dose and complete one follow-up visit.
- Discontinuation population: Patients who discontinue the use of Leuprorelin, are lost to follow-up, withdraw from the study or are dead.

### 13.6. Data analysis

All patients who have received at least one treatment after screening and had at least one available post-baseline data will be included in the analysis. All data will be analyzed descriptively based on the study design feature.

Continuous variables will be summarized using n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency and percentage.

Baseline information will be summarized, including demographic characters(age, sex, race as described by the subject, height, weight, growth rate, BMI, bone age, and concurrent medical conditions), medical history (including any significant conditions or diseases relevant to the disease under study that resolved at or prior to signing of informed consent, any medication relevant to eligibility criteria stopped at or within one month prior to signing of informed consent, any significant conditions or diseases relevant to the disease under study that resolved within 1 year prior to signing of informed consent, any medication relevant to eligibility criteria stopped at or within one month prior to signing of informed consent), estradiol, testosterone, GnRH-stimulated LH peak, GnRH-stimulated FSH peak, pubertal stage and gonads ultrasonic.

Drug exposure will be summarized by treatment duration with Leuprorelin.

Concomitant medication during the study will be summarized by preferred term of WHODRUG dictionary.



All analyses will be stratified by sex.

All analyses will be done based on observed data and no imputation will be done for missing data.

### 13.7. Analysis of the primary variable(s)

The primary variable will be analyzed using the percentage of subjects with peak LH suppression in GnRH stimulation (defined as LH peak value in GnRH stimualation $\leqslant$ 3.0 IU/L) at Week 24.

The percentage will be summarized by different visits and sex, and draw graphics to show tendency.

### 13.8. Analysis of the secondary variable(s)

In different sexs, the secondary variables will be summarized by the percentage of subjects with Tanner stage regression or no progression at Week 24 compared with Baseline; basal LH and FSH level of subjects at Baseline, Week 24, Week 36; the percentage of subjects

with decreased ratio of bone age over chronological age at Week 24 compared with Baseline; the percentage of subjects with decrease in first morning voided (FMV) urinary Gn at Week 24 compared with Baseline; incidence of treatment-emergent adverse events (TEAEs).

The safety analyses will be presented by frequency of AEs and SAEs by system organ class (SOC) and preferred term (PT), the severity of AEs and their relationship with Leuprorelin. Proportions of patients with AEs leading to dose down-titration, treatment interruption, and treatment discontinuation will be analyzed separately.

### 13.9. Discontinuation Analysis

The discontinuation analysis will be based on discontinuation population. The number and percentage of discontinuation due to adverse event or death and due to other reasons will be calculated separately. The tolerance of Leuprorelin will be evaluated by the discontinuation rate.

### 13.10. Analysis methods

Data collected in this study will be tabulated using descriptive statistics. Relevant statistical software (such as SAS 9.4) will be considered to support planned analyses.

### 13.11. Interim analysis.

This study will be subject to interim analysis at an appropriate time.

## 14. QUALITY CONTROL AND QUALITY ASSURANCE

### 14.1. Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the (e)CRFs. Source documents are defined as original documents, data, and records. The investigator and guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.



All aspects of the study and its documentation will be subject to review by the sponsor or the sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms, and review of (e)CRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

Alternative approaches may be used to ensure data quality, data integrity, and subject safety (eg, remote source data review/source data verification via phone or video) as permitted by regional and local regulations. Additional details are in the monitoring plan.

### 14.2. Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will

require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it may be reported to regulatory authorities as a serious breach of GCP and the protocol.

### 14.3. Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the United States [US] Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency [PMDA of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and guarantee access for quality assurance auditors to all study documents as described in Section 14.1.



## 15. ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" . The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

### 15.1. IRB

IRBs must be constituted according to the applicable requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study. The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will once the sponsor has confirmed the adequacy of site regulatory documentation no protocol activities, including screening may occur.

Study sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and sponsor.



### 15.2. Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed

consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.



### 15.3. Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth may be used to verify the subject and accuracy of the subject's unique identification number.

In the event that a serious data breach is detected, the sponsor or its designee and the investigator (as applicable) will take appropriate corrective and preventative actions in response. These actions will be documented and the relevant regulatory agency(ies) will be notified as appropriate. Where appropriate, the relevant individuals materially affected by the breach would also be notified; in the case of study subjects, this would be done through the investigator.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, UK MHRA, PMDA), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's [e]CRF).

## 15.4. Clinical Trial Disclosures and Publication

### 15.4.1. Clinical Trial Registration and Results Disclosure

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum, register all interventional clinical trials before study start and disclose the results of those trials in a manner and timeframe compliant with Takeda policy and all applicable laws and regulations. Clinical trial registration and results disclosures will occur on ClinicalTrials.gov, other clinical trial registries/databases as required by law, and on Takeda's corporate website(s).



### 15.4.2. Publication

During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication venue (eg, congress, journal) will appropriately reflect contributions to the production, review, and approval of the document.

## 15.5. Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

# 16. REFERENCES

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