Title: An Open label, Multicenter Study to Assess the Safety and Efficacy of Leuprorelin in the Treatment of Central Precocious Puberty

NCT Number: NCT02427958

Protocol Approve Date: 16 December2015

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

PROTOCOL

An Open label, Multicenter Study to Assess the Safety and Efficacy of Leuprorelin in the Treatment of Central Precocious Puberty

Leuprorelin-4001, Leuprorelin in the Treatment of Central Precocious Puberty

Sponsor: Takeda Development Center Asia, Pte. Ltd.
21 Biopolis Road
Nucleos North Tower, Level 4
Singapore 138567

Study Number: Leuprorelin-4001

IND Number: NA **EudraCT Number:** NA

Compound: Leuprorelin (Enantone)

Date: 16 December2015 **Amendment Number:** 1

Amendment History:

Date	Amendment Number	Amendment Type	Region
01 November 2014	Initial Protocol	Not applicable	China
16 December 2015	Amendment # 1	Substantial	China

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

TDC sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	China Contact
Serious adverse event and pregnancy reporting Medical Monitor (medical advice on protocol and compound) Responsible Medical Officer (carries overall responsibility for the conduct of the study)	PPD

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 clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 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

Electronic Signatures may be found on the last page of this document.

PPD

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, package insert 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, 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 Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B – Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D of this protocol.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Province)

_____

Location of Facility (Country)

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2.0 STUDY SUMMARY

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<tr><td colspan="2">Name of Sponsor(s):
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Leuprorelin</td></tr>
<tr><td>Title of Protocol:
An Open label, Multicenter Study to Assess the Safety and Efficacy of Leuprorelin in the Treatment of Central Precocious Puberty</td><td>IND No.:
Not Applicable</td><td colspan="2">EudraCT No.:
Not Applicable</td></tr>
<tr><td>Study Number:
Leuprorelin-4001</td><td colspan="3">Phase:
4</td></tr>
<tr><td colspan="4">Study Design:
This is a phase 4, open label study to be conducted in China, to assess long-term safety and efficacy of Leuprorelin in the treatment of central precocious puberty (CPP). Approximately 300 subjects will be enrolled. The treatment duration is 96 weeks. The study will consist of 3 periods including a 4-week Screening Period, a 96-week Treatment Period and a 4-week Safety Follow-up Period. After the end of the study, subjects will participate in an observational follow-up, in which subjects who remain on treatment will be observed at least every 24 weeks. All subjects will be followed up annually after the last dose until stable puberty is reached.</td></tr>
<tr><td colspan="4">Primary Objective:
To evaluate the safety of leuprorelin in subjects with CPP</td></tr>
<tr><td colspan="4">Secondary Objective:
To evaluate the efficacy of leuprorelin in subjects with CPP</td></tr>
<tr><td colspan="4">Subject Population:
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>
<tr><td colspan="2">Number of Subjects:
Estimated total: 300</td><td colspan="2">Number of Sites:
Approximately 10-15 sites in China</td></tr>
<tr><td colspan="2">Dose Level(s):
CPP subjects with body weight ≥20 kg will receive the recommended dose of leuprorelin 3.75 mg subcutaneous administration (SC) every 4 weeks. Subjects with body weight <20 kg will receive recommended dose of 1.88 mg SC every 4 weeks. It is not recommended to exceed 180 μg/kg.</td><td colspan="2">Route of Administration:
Subcutaneous</td></tr>
<tr><td colspan="2">Duration of Treatment:
96 weeks</td><td colspan="2">Period of Evaluation:
4 weeks Screening Period
96 weeks Treatment Period
4 weeks Safety Follow-up Period
Observational Follow-up until stable puberty is reached</td></tr>
<tr><td colspan="4">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.</td></tr>
</table>

- 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.
- The subject has onset of appearance of secondary sexual characteristic earlier than age 8.0 years in girls or earlier than 9.0 years in boys and the symptom is persistent, and has confirmed diagnosis of CPP.
- The subject has basal LH level >5.0 IU/L or peak LH>5.0 IU/L in stimulation test OR peak LH>3.3 IU/L with LH/follicle-stimulating hormone (FSH) >0.6 in stimulating test The subject has evidence of gonadal development evaluated by ultrasonography: multiple ovarian follicles ≥4 mm in any ovary OR uterine enlargement in females or testicular volume ≥4 mL in males.
- The subject has advanced bone age (BA) ≥1 year and BA is ≤11.5 years in females or ≤12.5 years in males or predicted adult height <150 cm in females or <160 cm in males OR SDS<-2 standard deviations (SD) OR rapid growth defined as growth of BA/growth of chronologic age >1. BA is determined by Greulich and Pyle standards or Tanner-Whitehouse 3 (TW3) standards.
- The subject has anticipated treatment duration of at least 2 year in investigator's judgment.

Main Criteria for Exclusion:

- The subject has received any investigational compound within 30 days prior to screening.
- The subject has received gonadotropin-releasing hormone analog (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, 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.

Main Criteria for Evaluation and Analyses:

The primary endpoint for this study is subject incidence of treatment-emergent adverse events (TEAE).

The secondary endpoint for this study is the percentage of subjects who have regression or no progression in Tanner staging at Week 96 compared with Baseline.

The other endpoints for this study are:

- Percentage of subjects with suppression of peak LH and FSH to pre-pubertal levels in stimulation test at Week 96
- Percentage of subjects with suppression of basal estradiol level in female subjects or testosterone level in male

subjects to pre-pubertal level at Week 96

- Percentage of subjects with improvement in predicted adult height at Week 96 compared with Baseline
- Percentage of subjects with a decrease in the ratio of BA to chronological age at Week 96 compared with Baseline
- Change in body mass index (BMI)
- Change in bone mineral density
- Incidence of polycystic ovarian syndrome in female subjects

Statistical Considerations:

- Analysis Sets

Safety Analysis Set

The Safety Analysis Set will consist of all subjects who are enrolled and received at least 1 dose of study drug.

Full Analysis Set

The Full Analysis Set (FAS) will consist of all subjects who are enrolled and received at least 1 dose of study drug.

- Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized. Summary statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous variables (eg, age and weight) and the number and percentage of subjects within each category will be presented for categorical variables (eg, sex, ethnicity, and race). Individual subject demographic and baseline characteristics data will be listed.

- Efficacy Analysis

The number and percentage of subjects who have regression or no progression in Tanner staging at Week 96 will be summarized. The number and percentage of subjects with suppression of peak LH and FSH after stimulation to pre-pubertal level at Week 96 compared with Baseline will be summarized. The number and percentage of subjects with suppression of basal estradiol level in female subjects or testosterone level in males subjects to pre-pubertal level at week 96 will be summarized. The number and percentage of subjects with improvement in predicted adult height at Week 96 compared with baseline will be summarized. The number and percentage of subjects with a decrease in the ratio of BA to chronological age at Week 96 compared with Baseline will be summarized.

Individual data will be listed.

- Safety Analysis

All adverse events (AEs) will be coded by system organ class (SOC), high level term, and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA). Treatment Emergent Adverse Events (TEAEs) are defined as AEs with onset occurring within 30 days (onset date – last date of dose +1≤ 30) after study drug administration. will be listed, and included in the summary tables. TEAEs will be summarized by treatment group by system organ class and preferred term. The following summary tables will be included in the report: summary of TEAEs and drug-related TEAEs, relationship of TEAEs to study drug (related vs. not-related), severity of TEAEs and related TEAEs. Data listings will be provided for all AEs including pretreatment event (PTE), TEAEs, AEs leading to study drug discontinuation, and serious adverse events serious adverse events (SAEs).

Incidence of polycystic ovarian syndrome in female subjects will be summarized.

- Other Variables

Safety laboratory data, vital signs, height, weight, BMI and electrocardiograms will be summarized along with other data collected in the case report form (eCRF).

Data collected during the observational follow-up period will be summarised and individual data will be listed.

Sample Size Justification:

This study is not statistically powered for any hypothesis testing. Approximately 300 subjects will be enrolled into the study from multiple centers across China. The sample size of 300 subjects is considered to be sufficient to fulfill the study objectives of the evaluation of safety and efficacy of Leuprorelin in the treatment of CPP as required by the China Food and Drug Administration (CFDA).

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

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 medication, 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 and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

AE	adverse event
AFP	alpha-fetoprotein
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-HCG	beta human chorionic gonadotropin
BA	bone age
bpm	beats per minute
BMI	body mass index
CEA	carcino-embryonic antigen
CFDA	China Food and Drug Administration
CPP	central precocious puberty
eCRF	electronic case report form
CRO	contract research organization
ECG	electrocardiogram
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
GnRH	gonadotropin-releasing hormone
GnRHa	gonadotropin-releasing hormone analog
hCG	human chorionic gonadotropin
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IND	Investigational New Drug
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
LFT	liver function test
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
PP	perprotocol
PT	preferred term
PTE	pretreatment event
QTc	corrected QT interval
SAE	serious adverse event

SAP	statistical analysis plan
SC	subcutaneous
SAS	safety analysis set
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse events
TW3	Tanner-Whitehouse 3
ULN	upper limit of normal
WHODRUG	World Health Organization Drug Dictionary

3.4 Corporate Identification

TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

Precocious puberty refers to appearance of secondary sexual characteristics in boys before 9 years and girls before 8 years. Children with central precocious puberty (CPP) have premature secretion and release of gonadotropin releasing hormone (GnRH) in the hypothalamus, activating secretion of gonadotropin by the pituitary gland, promoting development of the gonads and secretion of sex hormones, resulting in development of internal and external genital organs and appearance of secondary sexual characteristics [1].

The early onset of secondary characteristics can be psychologically and emotionally difficult for a young child. The young child does not understand the changes in his/her body and the emotional changes he or she is experiencing. The large size of the child due to the puberty growth spurt often causes further stress because of the greater expectations of parents and teachers because he/she seems older. Although intelligence and social skills do not advance with the child's size, he/she may be pushed ahead in school or in social situations because of this. The child is no longer like his/her peers, but rather a child's mind in a small adult body [2]. In China, the incidence of CPP is increasing. Epidemiology studies showed that the incidence of CPP in children aged 6-9 years in Zhejiang province is about 0.38% [3] and 1% in Shanghai [4]. The ratio of girls to boys is about 4-5 to 1 [4].

CPP is controlled by the hypothalamic-pituitary-gonadal axis, the same mechanism that controls normal puberty. If the reproductive hormonal cycle can be interrupted, the child can be returned to a prepubertal state. Halting this process means suppressing the pituitary so that gonadotropins will decrease to prepubertal levels. Due to the negative feedback mechanism, the gonads will follow suit, then, suppression of gonadotropins and sex steroids will trigger decreases in growth and bone maturation and will also halt the development of secondary sexual characteristics. GnRH analogs (GnRHa) have been the standard of care for CPP. Continuous exposure to GnRHa desensitizes pituitary gonadotroph receptors and suppresses luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion [1].

Leuprorelin (Enantone) is a GnRHa widely used in the treatment of CPP worldwide including China. It is a potent inhibitor of ganodotropin secretion by downregulation of the GnRH receptors in the pituitary gland when administered continuously in therapeutic dose. First administration results in an initial transient increase (hormonal flare), then a decrease in LH and FSH, leading to a reduction in serum testosterone and estradiol to prepubertal levels usually within 2 to 4 weeks after initiation of treatment. The reduction of gonadotropins and sex steroids during treatment with GnRH agonist in children with CPP allows for normal physical and psychological growth and development. The effects of GnRH agonists treatment are entirely reversible upon discontinuation of treatment and natural maturation occurs when gonadotropins return to pubertal levels following discontinuation of leuprolide acetate [5,6,7,8].

Two phase 3 studies were conducted in the United States to evaluate the efficacy and safety of leuprorelin in the treatment of CPP. The first study was an open label noncomparative study that utilized both the daily subcutaneous (SC) formulation and the depot formulation under the guidance of the individual investigator's Investigational New Drug (IND) and protocol [9]. The second study was also a phase 3, open, noncomparative study, but conducted under the sponsor's protocol and IND [9]. The studies were conducted at a total of 39 investigational sites. Two hundered twenty six (226) children were evaluated for efficacy and 365 for safety in these studies. In these investigations, children with CPP have been treated with leuprorelin injection or leuprorelin depot for periods of up to 4.9 and 2.7 years, respectively. The longest duration of treatment was 5.3 years, in a child who received both formulations. An initial dose of 50 ug/kg/day or 300 ug/kg/day once a month was recommended in the studies. In both studies, leuprorelin have been shown to be safe and effective in the suppression of gonadotropins and sex steroids in children with CPP who are properly diagnosed, aggressively treated and accurately monitored.

4.2 Rationale for the Proposed Study

The administration dose of leuprorelin differs in various countries, ranging from 10 to 350 μg/kg body weight [10, 11]. It was approved for CPP indication in China in 1998 at the dose of 30-90 μg/kg body weight every 4 weeks SC administration . However, recent clinical studies demonstrated that administration of leuprorelin at lower than 90 μg/kg body weight cannot achieve optimal pituitary desensitization in many patients. If incomplete suppression occurs during treatment, GnRHa administration may exacerbate disease progression and bone age (BA) increase, impairing long-term outcome. The dose greater than 90 μg/kg body weight was recommended in CPP treatment guideline issued by China Ministry of Health [12]. In 2013, China Food and Drug Administration (CFDA) approved the new dose of Leuprorelin at 30-180 μg/kg body weight SC every 4 weeks [13]. The approval was based on the results from the clinical trials conducted in the United States, Europe and a retrospective study in Japan [14]. There is a lack of long term safety and efficacy data of leuprorelin use in China. The main objective of this study is to collect the safety data in 300 CPP patients treated with leuprorelin after the approval of the new dose in China. Efficacy data will also be collected and evaluated.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

To evaluate the safety of leuprorelin in subjects with CPP.

5.1.2 Secondary Objective

To evaluate the efficacy of leuprorelin in subjects with CPP.

5.2 Endpoints

5.2.1 Primary Endpoint

Subject incidence of treatment-emergent adverse events (TEAE).

5.2.2 Secondary Endpoint

Percentage of subjects who have regression or no progression in Tanner staging at Week 96 compared with Baseline.

5.2.3 Additional Endpoints

- Percentage of subjects with suppression of peak LH and FSH to pre-pubertal levels in stimulation test at Week 96.
- Percentage of subjects with suppression of basal estradiol level in female subjects or testosterone level in male subjects to pre-pubertal level at Week 96.
- Percentage of subjects with improvement in predicted adult height at Week 96 compared with Baseline.
- Percentage of subjects with a decrease in the ratio of BA to chronological age at Week 96 compared with Baseline.
- Change in laboratory values including changes in chemistry, hematology and bone metabolism biomarkers.
- Change in body mass index (BMI).
- Change in bone mineral density.
- Incidence of polycystic ovarian syndrome in female subjects.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

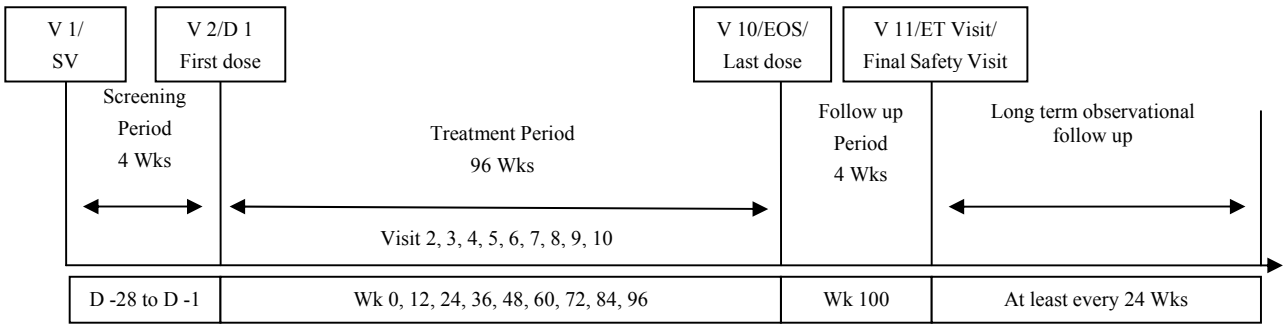
This is a phase 4, open label study to be conducted in China, to assess long-term safety and efficacy of leuprorelin in the treatment of CPP. Approximately 300 subjects will be enrolled. The treatment duration is 96 weeks. The study will consist of 3 periods including a 4-week Screening Period, a 96-week Treatment Period and a 4-week Safety Follow-up Period. Followed by an observational follow-up period where subjects who remain on treatment will be observed at least every 24 weeks and after last dose all subjects will be followed up annually until stable puberty is reached.

Eligible CPP subjects with body weight ≥20 kg will receive the recommended dose of leuprorelin 3.75 mg SC every 4 weeks. Subjects with body weight <20 kg will receive recommended dose of 1.88 mg SC every 4 weeks. It is not recommended to exceed 180 μg/kg. The dose can be adjusted based on subject's condition and investigator's judgment. Study visits, procedures, and evaluation are summarized in the Schedule of Study Procedures (Appendix A). Subjects will be followed until the end of the study, during which time they will be assessed by their treating physicians. serious adverse events (SAEs) and adverse events (AEs) will be recorded in the case report form (eCRF). Efficacy will be evaluated every 12 Weeks. The efficacy and safety data will be evaluated and submitted to CFDA.

Subjects will be given the first dose of study drug in the clinic at Day 1 (Visit 2, Week 0). The last dose of study drug will be given on the day of Week 96 (Visit 10). All dosing of study drug will take place in the clinic by appropriate site staff. End of study assessment will be conducted at Week 96 (Visit 10). All subjects who receive study drug will be required to have a Final Safety Visit (Visit 11) at approximately 4 weeks after the last dose.

After the end of the study, subjects will participate in a long term observational follow-up. During the observation follow-up period, the patient visits to the referring physician are not pre-specified by the study protocol, but will follow usual clinical practice. It is anticipated that the CPP patients will visit the site for check up at least every 24 weeks. All patient-care decisions, including diagnostic and therapeutic interventions, will be made by and conducted at the discretion of the participating study physicians according to their clinical judgement and the local standard of medical care. It is recommended to monitor patients every 12 to 24 weeks in the treatment guideline issued by China Ministry of Health [4]. The procedures are summarized in the Schedule of Study Procedures (Appendix A). All subjects will be followed up annually after the last dose of leuprorelin until stable puberty is reached. Stable puberty is defined as 96 weeks after menarche for girls, or secondary sexual characteristics development of Tanner staging V for boys. At each visit, the following data will be collect if it is reported in the patients medical record: Tanner staging evaluation, height and weight measurement, menstrual history assessment and pelvic ultrasonography for girls.

Figure 6.a Schematic of Study Design



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

A schedule of assessments is listed in Appendix A 错误!未找到引用源。.

6.2 Justification for Study Design, Dose, and Endpoints

The design proposed in this study is acceptable to evaluate the long term safety and efficacy of leuprorelin.

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. Leuprorelin is available in two strengths (3.75 mg and 1.88mg) for monthly administration in China. In many medical centers, it is administered at 3.75 mg every 4 weeks for patients with body weight ≥20 kg or 1.88 mg every 4 weeks for patients with body weight <20 kg. In a phase 3 trial conducted in 25 centers in Germany, a favorable efficacy and safety profile was demonstrated with this treatment regimen. Therefore, the recommended leuprorelin dose in this study is 3.75 mg every 4 weeks for patients with body weight ≥20 kg or 1.88 mg every 4 weeks for patients with body weight <20 kg, not exceeding 180 μg/kg. The dose can be adjusted based on physician's judgment. The inclusion/exclusion criteria are in alignment with Chinese and United States/European treatment guideline to ensure the treatment is given to the appropriate subjects.

The safety and efficacy 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 Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one 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 medication that indicates a change in the known risk/benefit profile for the compound/product, such that the risk/benefit 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.

6.3.2 Criteria for Premature Termination or Suspension of Investigational 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 Investigational 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 an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to randomization or 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. The subject has age of onset of appearance of secondary sexual characteristic earlier than age 8.0 years in girls or earlier than 9.0 years in boys and the symptom is persistent, and has confirmed diagnosis of CPP.
4. The subject has basal LH level >5.0 IU/L or peak LH>5.0 IU/L in stimulation test OR peak LH>3.3 IU/L with LH/follicle-stimulating hormone (FSH) >0.6 in stimulating test.The subject has evidence of gonadal development evaluated by ultrasonography: multiple ovarian follicles ≥4 mm in any ovary or uterine enlargement in females or testicular volume ≥ 4 mL in males.
5. The subject has advanced BA ≥ 1 year and BA is ≤ 11.5 years in females or ≤ 12.5 years in males OR predicted adult height <150cm in females or < 160 cm in males OR SDS<-2SD OR rapid growth defined as growth of BA /growth of chronologic age >1. BA is determined by Greulich and Pyle standards or Tanner-Whitehouse 3 (TW3) standards at screening.
6. The subject has anticipated treatment duration of at least 2 year in investigator's judgment.
7. 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.
8. 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 9.1.9 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.10 Pregnancy.

9. 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 test Day –1 or Day 1 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 9.1.16.

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 9.1.10.

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 0. 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. Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study medication refers to all or any of the drugs defined below.

Leuprorelin 3.75 mg, 1 vial per box (attached with 1 ampule of 1 ml vehicle for suspension per vial).

Leuprorelin 1.88 mg, 1 vial per box (attached with 1 ampule of 1 ml vehicle for suspension per vial).

8.1.1.1 Investigational drug

Leuprorelin 3.75 mg and 1.88 mg study medication are manufactured by Tianjin Takeda Pharmaceutical Company, Co., LTD. Tianjin, China.

Each box label will be compliant with requirements of the CFDA.

8.1.1.2 Sponsor-Supplied Drug

Sponsor-supplied drugs referenced in other sections of the protocol include the following:

Leuprorelin 3.75 mg, 1 vial per box (attached with 1 ampule of 1 ml vehicle for suspension per vial).

Leuprorelin 1.88 mg, 1 vial per box (attached with 1 ampule of 1 ml vehicle for suspension per vial).

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

This is a phase 4, open label study. The study will consist of 3 periods including a 4-week Screening Period, a 96-week Treatment Period and a 4-week Safety Follow-up Period.

During the Treatment Period, subjects with body weight ≥20 kg will receive the recommended dose of leuprorelin 3.75 mg SC every 4 weeks. Subjects with body weight <20 kg will receive recommended dose of 1.88 mg SC every 4 weeks. It is not recommended to exceed 180 ug/kg every 4 weeks. The dose can be adjusted based on physician'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 Day 1 (Visit 2). 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 3.75 mg and 1.88 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 3.75 mg and 1.88 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 3.75 mg and 1.88 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.

9.0 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. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

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 that informed consent is obtained; this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex and race as described by the subject of the subject at Screening (Visit 1).

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.7).

Medication history information to be obtained includes any medication relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 28 days 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 investigational 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; and (11) other. All subsequent physical examinations should assess clinically significant changes from the assessment prior to first dose examination.

9.1.4 Weight and Height

A subject should have weight and height measured while wearing indoor clothing and with shoes off.

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 medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (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 eCRF.

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. The condition (ie, diagnosis) should be described and recorded in the eCRF.

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.

Table 9.a Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
RBC WBC Hemoglobin Hematocrit Platelets	ALT Albumin Alkaline phosphatase AST Total bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase GGT Potassium Sodium Glucose Chloride Bicarbonate Calcium Magnesium	pH Specific gravity Protein Glucose Blood Nitrite Microscopic Analysis (only if positive dipstick results): RBC/high power field WBC/high power field Epithelial cells, casts etc

Other:
GnRH stimulation test
LH and FSH
Estradiol or testosterone
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.

(Please refer to Section 0 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN.)

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 10.2.3 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 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 are pre-menarche with no ovulation ability or have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) .

**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):

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

Intrauterine devices (IUDs):

- Copper T PLUS condom or spermicide.
- #Progesterone T PLUS condom or 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 female 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 (Appendix A). 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.

9.1.10 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 1.0.

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.

9.1.11 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.

9.1.12 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.

9.1.13 Bone Mineral Density

Bone mineral density will be evaluated by dual energy x-ray bone densitometry at selected sites only. Throughout the study, the same apparatus should be used and operated in the same scan mode for all scans for an individual subject. The results will be recorded in the eCRF.

9.1.14 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.

9.1.15 Pelvic/Testicular 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.

9.1.16 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.

9.1.17 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance into the treatment phase.

If the subject is found to be not eligible for treatment phase, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

Subjects will be injected the study medication Leuprorelin 3.75 mg or 1.88 mg on site by investigator or investigator's designee. All supplies used to administer study medication to the subject will be recorded on the eCRFs.

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 3.75 mg and 1.88 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 Appendix A. Assessments should be completed at the designated visit.

9.3.1 Screening - Visit 1

Subjects will be screened within 28 days prior to first dose (Week 0, Visit 2). Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.16 for procedures for documenting screening failures.

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

- Informed consent.
- Inclusion/exclusion criteria.
- Demographics, medical history, and medication history.
- Physical examination.
- Vital signs.
- Weight, height
- Concomitant medications.
- Concurrent medical conditions.
- Predicted adult height.

- Tanner staging evaluation.
- Bone age.
- Hematology, Urine analysis, clinical chemistry laboratoty tests.
- 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.
- Pelvic/testicular ultrasonography.
- Stimulation test.
- Cranial MRI.
- CEA, AFP, β-HCG.
- PTE assessment.
- Assign subject number.

9.3.2 Study Entrance - Visit 2 (Week 0, first dose)

Study entrance will take place on Day 1 (Visit 2). The following procedures will be performed and documented during Study Entrance:

- Vital signs.
- Weight, height
- Concomitant medications.
- Tanner staging evaluation.
- Urine Pregnancy test.
- 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.
- Bone mineral density.
- Serum bone metabolism biomarker.
- 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. The procedure for documenting Screening failures is provided in Section 9.1.16.

9.3.3 Treatment Phase - Visit 3 (Week 12)

Visit 3 will take place on Week 12. The following procedures will be performed and documented during this visit:

- Vital signs.
- Weight, height.
- Concomitant medications.
- Tanner staging evaluation.
- 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.
- Stimulation test.
- Injection of Investigational Drug by investigator or investigator's designee.
- AE assessment.

9.3.4 Treatment Phase - Visit 4 (Week 24)

Visit 4 will take place on Week 24. The following procedures will be performed and documented during this visit:

- Vital signs.
- Weight, height.
- Concomitant medications.
- Tanner staging evaluation.
- Bone age.
- Hematology.
- 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

- Clinical chemistry
- Pelvic/Testicular ultrasonography
- Estradiol or testosterone.
- Injection of investigational drug by investigator or investigator's designee
- AE assessment

9.3.5 Treatment Phase - Visit 5 (Week 36)

Visit 5 will take place on Week 36. The following procedures will be performed and documented during this visit:

- Vital signs.
- Weight, height.
- Concomitant medications.
- Tanner staging evaluation
- 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.
- LH and FSH.
- Estradiol or testosterone.
- Injection of investigational drug by investigator or investigator's designee
- AE assessment.

9.3.6 Treatment Phase - Visit 6 (Week 48)

Visit 6 will take place on Week 48. The following procedures will be performed and documented during this visit:

- Physical examination.
- Vital signs.
- Weight, height.
- Concomitant medications.
- Predicted adult height.
- Tanner staging evaluation.

- Bone age.
- Hematology.
- Urine analysis
- 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
- Clinical chemistry
- Pelvic/testicular ultrasonography.
- Estradiol or testosterone.
- Injection of investigational drug by investigator or investigator's designee
- AE assessment

9.3.7 Treatment Phase - Visit 7 (Week 60)

Visit 7 will take place on Week 60. The following procedures will be performed and documented during this visit:

- Vital signs.
- Weight, height.
- Concomitant medications.
- Tanner staging evaluation.
- 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.
- LH and FSH
- Estradiol or testosterone.
- Injection of investigational drug by investigator or investigator's designee.
- AE assessment.

9.3.8 Treatment Phase - Visit 8 (Week 72)

Visit 8 will take place on Week 72. The following procedures will be performed and documented during this visit:

- Vital signs.

- Weight, height.
- Concomitant medications.
- Tanner staging evaluation.
- Bone age.
- Hematology.
- 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.
- Clinical chemistry.
- Pelvic/testicular ultrasonography.
- Estradiol or testosterone.
- Injection of investigational drug by investigator or investigator's designee.
- AE assessment.

9.3.9 Treatment Phase - Visit 9 (Week 84)

Visit 9 will take place on Week 84. The following procedures will be performed and documented during this visit:

- Vital signs.
- Weight, height.
- Concomitant medications.
- Tanner staging evaluation.
- 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.
- LH and FSH.
- Estradiol or testosterone.
- Injection of investigational drug by investigator or investigator's designee.
- AE assessment.

9.3.10 Treatment Phase - Visit 10 (Week 96, last dose)

Visit 10 will take place on Week 96. The following procedures will be performed and documented during this visit:

- Vital signs.
- Weight, height.
- Concomitant medications.
- Predicted adult height.
- Tanner staging evaluation.
- Bone age.
- 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.
- Pelvic/testicular ultrasonography.
- Estradiol or testosterone.
- Stimulation test.
- Injection of investigational drug by investigator or investigator's designee.
- AE assessment.

9.3.11 Final Safety Visit or Early Termination - Visit 11 (Week 100)

Visit 11 will take place on Week 100. The following procedures will be performed and documented during this visit:

- Physical examination.
- Vital signs.
- Weight, height.
- Concomitant medications.
- Tanner staging evaluation.
- Hematology.
- Urine analysis.
- 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.
- Clinical chemistry.
- Pelvic/testicular ultrasonography.

- Estradiol or testosterone.
- Bone mineral density.
- Serum bone metabolism biomarker.
- AE assessment.

The Final Visit will be performed on Week 100 or at the Early Termination Visit. The following procedures will be performed and documented:

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

9.3.12 Observational Follow-up

Observational Follow-up will begin the first day after the Final safety Visit.

During the observation follow-up the patient visits to the referring physician are not pre-specified by the study protocol, but will follow usual clinical practice. It is anticipated that the CPP patients will visit the site for check up at least every 24 weeks. All patient-care decisions, including diagnostic and therapeutic interventions, will be made by and conducted at the discretion of the participating study physicians according to their clinical judgement and the local standard of medical care.

Data should be entered into the database, at the patients' visits (at least every 24 weeks) and at the end of data collection. However, no patients will be excluded based on different reporting frequencies. The source of the data is the patient medical record.

The following data will be recorded if it is collected as part of routine clinical practice:

- Physical examination.
- Vital signs.
- Weight, height.
- Predicted adult height.
- Tanner staging evaluation.
- Bone age.
- Hematology.
- Clinical chemistry.
- ECG.
- Pelvic/testicular ultrasonography.
- Estradiol or testosterone.

- AE assessment.

After the last dose of leuprorelin treatment, subjects will be followed up annually and conduct the following procedure until stable puberty is reached.

The following data will be recorded when it is collected as part of routine clinical practice:

- Tanner staging.
- Height and weight.
- Menstrual history for girls.
- Pelvic ultrasongraphy for girls.

The observational follow-up is not included in this study. The requirement has not been determined as yet. If long term observational follow-up is performed then the patients will undergo a further Consent process, including new Parent/Patient Information sheet.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; 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 finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the 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 underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

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 a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or 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 re-test and/or continued monitoring of an abnormal value 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 a PTE or as an AE.

Preexisting conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). 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 condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, 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 condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study medication, 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 severity of AEs /Serious PTEs:

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

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or 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 captured appropriately as a PTE or 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 PTEs or 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 PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

10.1.4 SAEs

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.
- Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

PTEs/AEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 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.

10.1.6 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.

10.1.7 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.

10.1.8 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.

10.1.9 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.

10.1.10 Frequency

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

10.1.11 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.

10.1.12 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 2) or until screen failure. For subjects who discontinue prior to study medication administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication (Visit 2). Routine collection of AEs will continue until 28 days after study visit 10, which will be Visit 11.

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 eCRF, 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.

Reporting of unexpected non-serious adverse drug reactions (ADRs):

For the non-serious AE which is not listed in the labeling, if it is potentially related to the study medication or study procedure, or if the causality is unknown/missed, the investigator should report this unexpected non-serious ADR to Takeda within 7 calendar days of fist notification of the event. The the AE page of the eCRF should be transmitted within 7 calendar days to the attention of the contact listed in Section 1.1. The investigator should make sure the success of the reporting transmission.

If the follow-up information of the unexpected non-serious ADR is received, the reporting of the follow-up information will follow the same reporting procedure of the initial report.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

A Takeda SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. 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 medication(s)
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1. The investigator should make sure the success of the reporting transmission.

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

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 Reporting of Abnormal Liver Function Tests

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 eCRF 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 eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately or within 24 hours of receipt. 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 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 or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs which 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

11.0 STUDY-SPECIFIC COMMITTEES

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

12.0 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 eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor 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. eCRFs must be completed in English. Data are transcribed directly onto eCRFs .

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 Takeda personnel (or designees) and will be answered by the site.

Corrections to eCRFs arerecorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change..Reasons for significant corrections should additionally be included.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

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

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. 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 eCRFs. The completed eCRFs 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 12.1 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),

electronic copy of eCRFs, including the audit trail, 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, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (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 Section 4.9.5 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 Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical 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.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted prior to database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

A SAP will be prepared for the observational follow-up period.

13.1.1 Analysis Sets

Safety Analysis Set

The Safety Analysis Set (SAS) will consist of all subjects who are enrolled and received at least 1 dose of study drug.

Full Analysis Set

The Full Analysis Set (FAS) will consist of all subjects who are enrolled and received at least 1 dose of study drug.

Per Protocol Analysis Set

The Per Protocol (PP) Analysis Set will consist of subjects who are in the FAS and have no major protocol violations.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized. Summary statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous variables (eg, age and weight) and the number and percentage of subjects within each category will be presented for categorical variables (eg, sex, ethnicity, and race). Individual subject demographic and baseline characteristics data will be listed.

Medical history, concurrent medical conditions and concomitant medications will be summarized and listed.

13.1.3 Efficacy Analysis

The number and percentage of subjects who have regression or no progression in Tanner staging at Week 96 will be summarized, individual data will be listed. The number and percentage of subjects with suppression of peak LH and FSH after stimulation to pre-pubertal level at Week 96 will be summarized, individual data will be listed. The number and percentage of subjects with suppression of basal estradiol level in female subjects or testosterone level in male subjects to

pre-pubertal level at Week 96 will be summarized, individual data will be listed. The number and percentage of subjects with improvement in predicted adult height at Week 96 compared with Baseline will be summarized, individual data will be listed. The number and percentage of subjects with a decrease in the ratio of bone age to chronological age at Week 96 compared with Baseline will be summarized, individual data will be listed. For binary data where appropriate 95% confidence intervals will be presented.

13.1.4 Safety Analysis

For all safety endpoints, Baseline is defined as the last non-missing measurement prior to first dose of study drug. Safety data will be summarized using the safety analysis set.

13.1.4.1 Adverse Events

All AEs will be coded by system organ class (SOC), high level term, and preferred term (PT) using MedDRA. TEAEs are defined as AEs with onset occurring within 30 days (onset date – last date of dose +1≤ 30) after study drug administration. will be listed, and included in the summary tables. TEAEs will be summarized by treatment group by system organ class and preferred term. The following summary tables will be included in the report: summary of TEAEs and drug-related TEAEs, relationship of TEAEs to study drug (related vs. not-related), severity of TEAEs and related TEAEs. Data listings will be provided for all AEs including PTE, TEAEs, AEs leading to study drug discontinuation, and SAEs.

Incidence of polycystic ovarian syndrome in female subjects will be summarized.

13.1.4.2 Safety Laboratory Evaluation

Individual results of safety laboratory tests from hematology, chemistry, and urinalysis that meet Takeda's markedly abnormal criteria will be summarized and listed. Baseline, postdose, and change from Baseline to postdose laboratory data will be summarized. All clinical laboratory data will be listed.

13.1.4.3 Vital Signs

Individual results of vital signs that meet Takeda's markedly abnormal criteria will be summarized and listed. Baseline, postdose, and changes from Baseline in vital sign measurements will be summarized. All vital sign data will be provided in the data listings.

13.1.4.4 Height, Weight and BMI

Baseline, postdose, and changes from Baseline in height, weight and BMI measurements will be summarized. All data for height, weight, BMI will be provided in the data listings.

13.1.4.5 ECG

Individual results of quantitative ECG parameters from the 12-lead safety ECGs that meet TDC's markedly abnormal criteria will be summarized and listed. Baseline, postdose, and changes from

Baseline in quantitative ECG parameters will be summarized. Shift tables will be generated for the investigator's ECG interpretations that changed from Baseline to the postdose collections by above groups. Analysis of central tendency for QT/corrected QT interval (QTc) and categorical analysis of QT/QTc will be performed. All ECG data will be provided in the data listings.

13.1.5 Other Analysis

The serum bone metabolism biomarkers including phosphorus, 25-hydroxy vitamin D, osteocalcin, crosslaps will be summarized by Baseline, postdose and changes from Baseline, individual data will be listed.

Baseline, postdose, and changes from Baseline in bone mineral density measurements will be summarized. All bone mineral density data will be provided in the data listings.

Pelvic and testicular ultrasonography will be summarised and data will be provided in listings.

Other Variables:

The physical examination findings will be presented in data listings.

The urine pregnancy test, cranial MRI, CEA, AFP and β-HCG at Screening will be summarised and listed.

Data collected during the observational follow-up phase will be summarised and individual data will be listed.

13.2 Interim Analysis and Criteria for Early Termination

One interim analysis will be performed after Week 100 visit. All available efficacy and safety data will be evaluated and reported to CFDA. The study will be continued to the observational safety follow-up phase.

13.3 Determination of Sample Size

This study is not statistically powered for any hypothesis testing. Approximately 300 subjects will be enrolled into the study from multiple centers across China. The sample size of 300 subjects is considered to be sufficient to fulfill the study objectives of the evaluation of safety and efficacy of Leuprorelin in the treatment of CPP as required by the CFDA.

14.0 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 eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution 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 designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, 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 eCRFs 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.

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. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from 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 Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 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" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable local 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 or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC 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 or IEC for approval. The IRB's or IEC'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 (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC 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. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC 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 or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC 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 study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with China GCP, ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, CFDA, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs 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 eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. 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. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

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 will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

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 interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

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 clinical study subjects. Refer to the Clinical 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.

16.0 REFERENCES

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Appendix A Schedule of Study Procedures

	Screening	Treatment										
Study Day/Week:	**Days -28 to -1**	**Wk 0/ Day 1/first dose (a)**	**Wk 12**	**Wk 24**	**Wk 36**	**Wk 48**	**Wk 60**	**Wk 72**	**Wk 84**	**Wk 96/ last dose**	**Final safety Visit/ Early Termination Visit Week 100 (b)**	**Observational Follow-up visit (c)**
Visit Windows (Days):	**NA**	**NA**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Informed consent	X											
Inclusion/exclusion criteria	X											
Demographics and medical history	X											
Medication history	X											
Physical examination	X					X					X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Weight and height	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	
Concurrent medical conditions	X											
Predicted adult height (d)	X					X				X		X
Tanner staging evaluation	X	X	X	X	X	X	X	X	X	X	X	X
Bone age (e)	X			X		X		X		X		X
Hematology	X			X		X		X			X	X
Urine analysis	X					X					X	
Urine Pregnancy test (f)		X										
Pregnancy avoidance counseling	X	X	X	X	X	X	X	X	X	X	X	
Clinical chemistry	X			X		X		X			X	X
ECG	X		X		X		X			X		X
Pelvic/Testicular ultrasonography (g)	X			X		X		X		X	X	X
LH and FSH					X		X		X			
Estradiol or Testosterone		X(j)	X	X	X	X	X	X	X	X	X	X
Stimulation test (h)	X		X							X		
Cranial MRI (i)	X											
CEA, AFP, β-HCG	X											
Bone mineral density (j)		X (j)									X	
Serum bone metabolism biomarker (k)		X(j)									X	
Injection investigational drug (l)		X	----	----	----	----	----	----	----	X		
PTE assessment	X	X										
AE assessment		X	X	X	X	X	X	X	X	X	X	X

NA=not applicable.

(a) The day of first investigational drug administration for Treatment period is Day 1. The day before first investigational drug administration for Treatment period is Day -1.

(b) Conduct Final Visit procedures for subjects discontinued early per Section 7.6. The end of study is defined as the date of the last visit (Week 100) of the last subject undergoing the study unless the study is stopped earlier by sponsor due to futility or for safety reasons. Subjects who discontinued from the study for any reason will complete the Early Termination Visit/Final Safety Visit , 4 weeks after the last dose of leuprorelin.

(c) During the observational follow- up period, it is recommended to monitor the subjects who remain on treatment at least every 6 months or at a schedule based on the investigator's judgments until drug discontinuation to collect the following: height and weight, secondary sexual characteristics, hematology, clinical chemistry, ultrasonography, LH and FSH, estradiol or testosterone and ECG. ECG will also be performed 4 weeks after the last administration of leuprorelin. All subjects will be followed up annually after the last dose of leuprorelin until stable puberty is reached. At each visit, the following will be performed: Tanner staging, height and weight, BMI, menstrual history, and pelvic ultrasonography for girls. Stable puberty is defined as 2 years after menarche for girls or Tanner staging V of secondary sexual characteristics development for boys.

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

(e) 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

(f) 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.

(g) 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.

(h) Stimulation test: Blood samples will be collected at 0, 30, and 60, 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. (i) Cranial MRI can consist of only pituitary scan, including saddle region.

(j) Bone mineral density will be evaluated by dual energy x-ray bone densitometry at selected sites, which can done at any time prior to the first dose after the Screening. Estradiol or Testosterone and Serum bone metabolim biomark also can be done at any time prior to first dose as part of screening visit. (k) Serum bone metabolism biomarker included phosphorus, 25-hydroxy vitamin D, osteocalcin, crosslaps. These 4 tests can be performed as per what is available at the given Site. These tests can done at any time prior to the first dose after the Screening.

(l) Subcutaneous injection Leuprorelin every 4 weeks. For the dosing visits between Visits 2-3, between Visits 3-4, between Visits 4-5, between visits 5-6, between visits 6-7, between 7-8, between 8-9, between visits 9-10: these visit window is +/- 2 days; in addition, the between gap between dosing cannot be less than 3 weeks (21 days).

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (non routine/non standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.

19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and

e) that the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use adequate contraception (as defined in the informed consent) from Screening throughout the duration of the study. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study medication will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use adequate contraception (as defined in the informed consent) from Screening throughout the duration of the study. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.