



Title: An Observational, Retrospective Study to Evaluate the Long Term Safety and Effectiveness of Leuporelin in the Treatment of Central Precocious Puberty

NCT Number: NCT02993926

Protocol Approve Date: 26 January 2018

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

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**NON-INTERVENTIONAL SAFETY STUDY
PROTOCOL**

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1.0 TITLE

An Observational, Retrospective Study to Evaluate the Long Term Safety and Effectiveness of Leuprorelin in the Treatment of Central Precocious Puberty

Study Number: Leuprorelin-5001

Version Number: Amendment no. 01, 26 January 2018

1.1 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 (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures are provided 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 12.0 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- [Appendix A](#)– Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in [Appendix B](#) 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 LIST OF ABBREVIATIONS

AE	adverse event
ADR	adverse drug reaction
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BA/CA	bone age/chronological age
BMD	bone mineral density
BMI	body mass index
CFDA	China Food and Drug Administration
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CPP	central precocious puberty
CRF	case report form
CRO	contract research organization
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 analogs
GPP	Good Pharmacoepidemiology Practices
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
ISPE	International Society for Pharmacoepidemiology
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
PMDA	Pharmaceuticals and Medical Devices Agency
QTc	corrected QT interval
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SOC	system organ class
WBC	white blood cell
WHODRUG	World Health Organization Drug Dictionary

3.0 MARKETING AUTHORIZATION HOLDER / SPONSOR

Marketing Authorization holder:

Takeda Pharmaceutical Company Limited,
1-1, Doshomachi 4-chome, Chuo-ku, Osaka Japan

Sponsor:

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

4.0 RESPONSIBLE PARTIES

Contact Type/Role	China Contact
Serious Adverse Event Reporting	PPD
Medical Monitor (medical advice on protocol and compound)	
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	
Leading Principal Investigator	

5.0 ABSTRACT

Title

An Observational, Retrospective Study to Evaluate Long Term Safety and Effectiveness of Leuprorelin in the Treatment of Central Precocious Puberty

Rationale and Background

Precocious puberty refers to appearance of secondary sexual characteristics in boys before 9 years and girls before 8 years [1]. 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]. Treatment goals include hormonal suppression, cessation of development of secondary sex characteristics, halting or preventing menarche, and preservation of adult height [1][2]. If left untreated, children with CPP can also face psychological challenge resulting from premature physical maturation that contrasts with their immature emotional development [2].

GnRH analogs (GnRHa) have been the standard of care for CPP [1]. Continuous exposure to GnRHa desensitizes pituitary gonadotropin receptors and suppresses luteinizing hormone (LH) and follicle stimulating hormone (FSH) secretion [2].

Leuprorelin acetate (trade name: ENANTONE) is a GnRHa widely used in the treatment of CPP. It was approved for CPP indication in China in 1998 at the dose of 30-90 µg/kg body weight subcutaneously administration every 4 weeks. However, recent clinical studies demonstrated that administration of leuprorelin acetate at lower than 90 µg/kg body weight cannot achieve optimal pituitary desensitization in many patients. If incomplete suppression is operative during treatment, GnRHa administration may exacerbate disease progression and bone age increase, impairing long-term outcome [3]. The dose greater than 90 µg/kg body weight was recommended in CPP treatment guideline issued in 2010 by the Ministry of Health of China and Consensus on Diagnosis and Treatment of Central Precocious Puberty (2015) [4][5].

In 2013, China Food and Drug Administration (CFDA) approved the new dose of leuprorelin acetate at 30-180 µg/kg body weight, subcutaneous (SC), every 4 weeks [6]. The approval was based on results from the clinical trials of leuprorelin acetate conducted in US and Europe and a retrospective study in Japan [7][8]. There is a lack of safety and effectiveness data of leuprorelin acetate long term use in China. This retrospective, medical chart review study is designed to evaluate and compare descriptively the effectiveness and safety of high dose (≥ 90 µg/kg up to 180 µg/kg) and low dose (< 90 µg/kg down to 30 µg/kg) leuprorelin acetate in China.

Research Question and Objectives

The goal of this study is to evaluate the safety and effectiveness of leuporelin acetate in CPP treatment in China.

Objective 1: To describe the safety of high dose leuporelin acetate (≥ 90 $\mu\text{g/kg}$ up to 180 $\mu\text{g/kg}$) and low dose leuporelin acetate (< 90 $\mu\text{g/kg}$ down to 30 $\mu\text{g/kg}$) in CPP treatment of at least 9 continuous months of ENANTONE

Objective 2: To describe the long term effectiveness of high dose leuporelin acetate (≥ 90 $\mu\text{g/kg}$ up to 180 $\mu\text{g/kg}$) and low dose leuporelin acetate (< 90 $\mu\text{g/kg}$ down to 30 $\mu\text{g/kg}$) in CPP treatment of at least 9 continuous months of ENANTONE

Study Design

Observational retrospective medical chart review study.

Population

Patients with central precocious puberty treated with ENANTONE for at least 9 continuous months duration, initiated and received the last dose of ENANTONE treatment during the index period from 1 September 1998 to 30 September 2018 in multiple centers across China. Patients who were treated with other GnRHa (including generic leuporelin acetate) after the 9-months treatment with ENANTONE can be enrolled into the study.

Outcomes

Primary Outcomes

- 1) Safety - Adverse events (AEs) and serious adverse events (SAEs) reported by physicians in the medical records (eg, incidence of any injection site reaction) during and after treatment with ENANTONE
- 2) Effectiveness - Regression or no progression in Tanner staging during and after treatment with ENANTONE

Secondary Outcomes

- 1) LH and FSH suppression to prepubertal level during and after treatment with ENANTONE
- 2) Estradiol or testosterone level suppression during treatment with ENANTONE
- 3) Decrease in the ratio of bone age to chronological age (BA/CA ratio) during treatment with ENANTONE

Additional Outcomes

- 1) Increase in predicted adult height during and after treatment with ENANTONE
- 2) Change from baseline in standard laboratory tests during and after treatment with ENANTONE
- 3) Incidence rate of polycystic ovarian syndrome during and after treatment with ENANTONE
- 4) Evaluation of the long term effect on reproduction
- 5) Change from baseline in bone mineral density (BMD) during and after treatment with ENANTONE
- 6) Change from baseline in body mass index (BMI) during and after treatment with ENANTONE

Data Sources

The retrospective study will be undertaken in China using the medical records of CPP patients from geographically distributed hospitals in both northern and southern China.

Study Size

Approximately 300 subjects (planned)

Data Analyses

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

6.0 AMENDMENTS AND UPDATES

This document describes the changes in reference to the Protocol Incorporating Amendment No. 01.

The primary purpose of this amendment is to revise the objectives, outcomes and inclusion/exclusion criteria to allow patients who were treated with GnRHa other than ENANTONE after the ENANTONE treatment to be enrolled into the study, provided that they have been treated with at least 9 continuous months of ENANTONE during the index period. Also, the index period is extended by 1 year from the original plan to enable further enrollment of patients.

Number	Section of study protocol	Amendment or update	Reason
1	Section 1.1 Approval	Updated the signatories.	To reflect the latest team membership.
2	Section 4.0 Responsible Parties	Updated the contact information.	To reflect the latest team membership.
3	Section 7.0 Milestones	Updated the actual dates for start of data collection and public disclosure.	To reflect the latest study progression.
4	Section 9.0 Research Question and Objectives (a)	Revised the wording for Objectives 1 and 2.	To reflect the change in study population (as described in row #5 of this table).
5	Section 10.1 Study Design (a)	Revised the study population requirement.	To allow patients who were treated with GnRHa other than ENANTONE after the ENANTONE treatment to be enrolled into the study provided that they have been treated with at least 9 continuous months of ENANTONE during the index period.
6	Section 10.1 Study Design (a)	Added detailed description and diagram on the study design.	To clarify the definition of each study phase and time points.
7	Section 10.1 Study Design (a)	Extended the end of the index period from 30 September 2017 to 30 September 2018.	To allow further enrollment of patients into the study.
8	Section 10.1 Study Design (a)	Added detailed description on dose groups.	To clarify how the patients will be categorized into each dose group.
9	Section 10.2.1 Outcomes (a)	Redefined the Secondary Outcomes by re-categorizing Secondary Outcomes #4 to #9 in the original protocol into Additional Outcomes #1 to #6.	To clarify the priority of the outcomes.
10	Section 10.2.1 Outcomes (a)	Removed the Secondary Outcome # 10 (Injection site reaction during the treatment phase) in the original protocol.	The assessment of injection site reaction is included in the Primary Outcome #1 (Safety).

(a) Section 5.0 (Abstract) also revised accordingly.

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Number	Section of study protocol	Amendment or update	Reason
11	Section 10.2.2 Variables to be Collected	New section created.	To clarify the types of variables to be collected.
12	Section 10.2.3 Variables Collected During Each Study Phase	New section created.	To clarify the variables to be collected during each study phase.
13	Section 10.4.1 Inclusion Criteria	Revised inclusion criteria #2, #3, #4 and #5.	To reflect the change in study population and index period (as described in rows #5 and #7 of this table).
14	Section 10.4.2 Exclusion Criteria	Revised exclusion criteria #1 and #2.	To reflect the change in study population (as described in row #5 of this table).
15	Section 10.7 Data Analysis	Revised the description of data analysis plan.	To reflect the change in study population (as described in row #5 of this table), and for clarification.
16	Section 10.7.1 Analysis Sets	Revised the definition of Per Protocol Set.	To reflect the change in study population (as described in row #5 of this table).
17	Section 10.7.3 Effectiveness Analysis	Revised the description of covariates on BMI analysis.	To revise typo.
18	Section 10.8.2 Protocol Deviations	Added description on protocol deviation rule.	To clarify that missing data for non-mandatory variables will not be handled as protocol deviation.
19	Throughout the protocol	Revised/edited texts (including grammatical and editorial changes).	For clarification purposes.

(a) Section 5.0 (Abstract) also revised accordingly.

7.0 MILESTONES

Milestone	Planned Date	Actual Date	Comments
Draft protocol to PRC	07 July 2016	07 July 2016	NA
Protocol approval	30 Sep 2016	10 Oct 2016	NA
Start of data collection	31 Dec 2016	24 Jun 2017	NA
End of data collection	30 Jun 2018	To be determined	NA
Public Disclosure	31 Oct 2016	13 Dec 2016	NA
Final study results	30 Sep 2018	To be determined	NA
Final report of study results	31 Dec 2018	To be determined	NA

8.0 RATIONALE AND BACKGROUND

Precocious puberty refers to appearance of secondary sexual characteristics in boys before 9 years and girls before 8 years [1]. Children with CPP have premature secretion and release of 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]. Treatment goals include hormonal suppression, cessation of development of secondary sex characteristics, halting or preventing menarche, and preservation of adult height [1][2]. If left untreated, children with CPP can also face psychological challenge resulting from premature physical maturation that contrasts with their immature emotional development [2].

GnRHa have been the standard of care for CPP [1]. Continuous exposure to GnRHa desensitizes pituitary gonadotropin receptors and suppresses LH and FSH secretion [2].

ENANTONE is a GnRHa widely used in the treatment of CPP. It was approved for CPP indication in China in 1998 at the dose of 30-90 µg/kg body weight subcutaneously administration every 4 weeks. However, recent clinical studies demonstrated that administration of leuprorelin acetate at lower than 90 µg/kg body weight cannot achieve optimal pituitary desensitization in many patients. If incomplete suppression is operative during treatment, GnRHa administration may exacerbate disease progression and bone age increase, impairing long-term outcome [3]. The dose greater than 90 µg/kg body weight was recommended in CPP treatment guideline issued in 2010 by the Ministry of Health of China and Consensus on Diagnosis and Treatment of Central Precocious Puberty (2015) [4][5].

In 2013, CFDA approved the new dose of leuprorelin acetate at 30-180 µg/kg body weight, SC, every 4 weeks [6]. The approval was based on results from the clinical trials of leuprorelin acetate conducted in US and Europe and a retrospective study in Japan [7][8]. There is a lack of safety and effectiveness data of leuprorelin acetate long term use in China. This retrospective, medical chart review study is designed to evaluate and compare descriptively the effectiveness and safety of high dose (≥ 90 µg/kg up to 180 µg/kg) and low dose (< 90 µg/kg down to 30 µg/kg) leuprorelin acetate in China.

9.0 RESEARCH QUESTION AND OBJECTIVES

The goal of this study is to evaluate the safety and effectiveness of leuprorelin acetate in CPP treatment in China.

Objective 1: To describe the safety of high dose leuprorelin acetate ($\geq 90 \mu\text{g/kg}$ up to $180 \mu\text{g/kg}$) and low dose leuprorelin acetate ($<90 \mu\text{g/kg}$ down to $30 \mu\text{g/kg}$) in CPP treatment of at least 9 continuous months of ENANTONE

Objective 2: To describe the long term effectiveness of high dose leuprorelin acetate ($\geq 90 \mu\text{g/kg}$ up to $180 \mu\text{g/kg}$) and low dose leuprorelin acetate ($<90 \mu\text{g/kg}$ down to $30 \mu\text{g/kg}$) in CPP treatment of at least 9 continuous months of ENANTONE

10.0 RESEARCH METHODS

10.1 Study Design

10.1.1 Study Population and Design

This is an observational, retrospective study to evaluate long term safety and effectiveness of ENANTONE (leuporelin acetate) in the treatment of CPP.

Approximately 300 patients with CPP, who were treated with ENANTONE for at least 9 continuous months, who initiated and received the last dose of treatment during the index period from 1 September 1998 to 30 September 2018, will be enrolled into the study. Patients who were treated with other GnRH α (including generic leuporelin acetate) after the 9-months treatment with ENANTONE can be enrolled into the study. Within each site, sequential eligible patients will be enrolled until the site's patient quota has been reached. Medical records will be collected and reviewed.

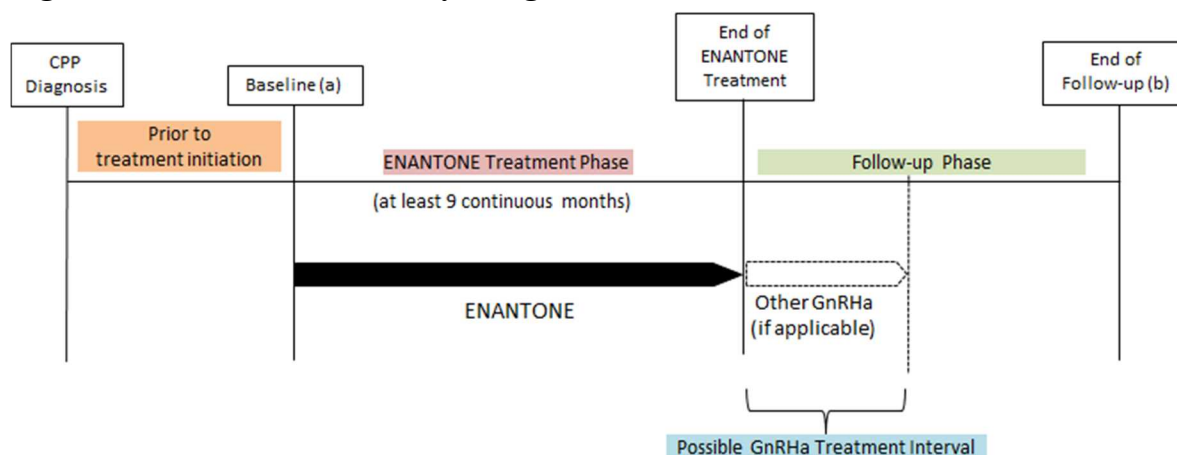
Prior to ENANTONE treatment initiation, all relevant data (specified in Section [10.2.3.1](#)), including data pertaining to the diagnosis of CPP will be collected at all available time points.

The **ENANTONE Treatment Phase** is the period during which patients were treated with at least 9 continuous months of ENANTONE. All relevant data (specified in Section [10.2.3.2](#)) will be collected at all available time points.

The **Follow-up Phase** is the period after the ENANTONE Treatment Phase up to the day of last available follow-up data for the subject. All relevant data (specified in Section [10.2.3.2](#)) will be collected at all available time points after the ENANTONE Treatment Phase. At a minimum, the data from the most recent time point available in the medical record should be included so as to include data on long term follow up of the subject. During the Follow-up Phase, a GnRH α Treatment Interval may apply to those patients who were treated with a GnRH α other than ENANTONE (either generic leuporelin acetate or other GnRH α) for CPP; in this case, the dates of therapy with this other GnRH α should be noted in the case report form (CRF).

The study design is shown in [Figure 10.a](#).

Figure 10.a Overview of Study Design



(a) Baseline: First day of administration of ENANTONE.

(b) End of Follow-up: The day of last available follow-up data for the subject.

10.1.2 Exposure

During the ENANTONE Treatment Phase, patients should have received at least 9 continuous months treatment with ENANTONE. According to the dose of ENANTONE the patient first received at Baseline and the weight of the patient at Baseline, each patient will be categorized to either one of the following dose groups:

- Low dose group: subcutaneous injection of ENANTONE $<90 \mu\text{g/kg}$ down to $30 \mu\text{g/kg}$
- High dose group: subcutaneous injection of ENANTONE $\geq 90 \mu\text{g/kg}$ up to $180 \mu\text{g/kg}$

10.2 Variables

10.2.1 Outcomes

Primary Outcomes

- 1) Safety –Adverse events (AEs) and serious adverse events (SAEs) reported by physicians in the medical records (eg, incidence of any injection site reaction) during and after treatment with ENANTONE
- 2) Effectiveness - Regression or no progression in Tanner staging during and after treatment with ENANTONE

Secondary Outcomes

- 1) LH and FSH suppression to prepubertal level during and after with ENANTONE
- 2) Estradiol or testosterone level suppression to prepubertal level during and after treatment with ENANTONE

- 3) Decrease in the ratio of bone age to chronological age (BA/CA ratio) during treatment with ENANTONE

Additional Outcomes

- 1) Increase in predicted adult height during and after treatment with ENANTONE
- 2) Change from baseline in standard laboratory tests during and after treatment with ENANTONE
- 3) Incidence rate of polycystic ovarian syndrome during and after treatment with ENANTONE
- 4) Evaluation of long term effect on reproduction
- 5) Change from baseline in BMD during and after treatment with ENANTONE
- 6) Change from baseline in BMI during and after treatment with ENANTONE

10.2.2 Variables to be Collected

The following variables may be collected and recorded on the CRF as are available in the subject's chart. At a minimum, data related to the primary and secondary endpoints should be collected. This includes data at time of diagnosis of CPP, at the beginning of the ENANTONE Treatment Phase, at the end of the ENANTONE Treatment Phase and at the most recent time in the Follow-up Phase.

10.2.2.1 Informed Consent

Each patient or, when applicable, the subject's legally acceptable representative must provide written informed consent before any study-required data are collected.

10.2.2.2 Patient Demographics

The date of birth, gender and family origin (North China/South China) of the patient will be recorded.

10.2.2.3 Disease History

The onset date of appearance of secondary characteristics and the CPP diagnosis date will be recorded.

10.2.2.4 BMD

The z-score for BMD and the anatomical site of measurement will be recorded. The BMD is typically determined using dual-energy X-ray absorptiometry, but BMD determined with any apparatus/mode is acceptable for collection.

10.2.2.5 Bone Age, Growth Rate and BA/CA Ratio

Bone age (years and presence of any abnormalities) and growth rate will be recorded.

BA/CA ratio will be calculated by the sponsor from the bone age and chronological age (derived from the date of birth, date when the X-ray was performed to assess bone age and the radiologic evaluation of bone age as available in the subject's chart all of which will be recorded in the CRF). The calculated BA/CA results will not be recorded in the CRF.

10.2.2.6 Height, Predicted Adult Height, Weight and BMI

Height, predicted adult height and weight will be recorded.

The predicted adult height is preferably derived by the Tanner-Whitehouse 3 method; where not possible, Bayley-Pinneau method or other methods are also acceptable.

The BMI will be calculated by the sponsor from the patient's weight and height recorded in the CRF. The calculated BMI results will not be recorded in the CRF.

10.2.2.7 Medical History and Comorbidities

The start/stop date of any medical history and/or comorbidities and whether any medication was given for the condition will be recorded. Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease throughout the duration of the study and also prior to signing of informed consent.

10.2.2.8 Prior and Concomitant Medications

The dose and route of administration, start/stop date (including information on whether or not the start date was before the first dose of ENANTONE), and indication name of any medications used by the patient will be recorded.

10.2.2.9 Evaluation of Long Term Effect on Reproduction

The long term effect of GnRH agonist therapy on reproduction will be evaluated by the change in several parameters related to sexual maturity and if available fertility. These measures will be collected and qualitatively evaluated as available. These parameters include but may not be limited to measures such as changes in ovarian volume, follicle counts, presence and regularity of menstrual cycle in females, testicular volume in males, changes in the sex hormones in both sexes (LH, FSH, estradiol [female], testosterone [male]), and or elevated human chorionic gonadotropin beta subunit (β -HCG) in females and pregnancy and live births for both sexes.

Pelvic Measurement

The following data will be recorded:

- Female patients: uterus length, ovarian volume, maximum follicle size, follicles number (left/right)
- Male patients: testicular volume (left/right)

Menstruation Cycles (Females)

For female patients, the age of menarche, rhythm of menstrual cycle (days) and menstrual quantity (normal/more than normal/less than normal) will be recorded.

Sexual Characteristic Examination

The following data will be recorded:

- Female patients: pubic hair (Tanner staging), breast (Tanner staging)
- Male patients: pubic hair (Tanner staging), beard, prominent Adam's apple, voice change

Hormonal Measurements

The following data will be recorded:

LH, FSH, estradiol (female), testosterone (male)

β -HCG (Females)

Results of either serum or urine β -HCG will be recorded.

Pregnancy

If there is record of patient's or the partner of the patient's pregnancy, the following data will be recorded: date of last menstrual period before pregnancy, confirmation date of the pregnancy, estimated date of delivery (if applicable), outcome (live birth/therapeutic abortion/spontaneous abortion/stillbirth/neonatal death), number of births (and past birth dates if applicable).

10.2.2.10 Tanner Staging

Tanner staging data (breast [female], genitals [male], pubic hair [female/male]) will be recorded.

10.2.2.11 Cranial CT/MRI

Cranial CT/MRI results will be recorded.

10.2.2.12 Clinical Laboratory Test

Results of the parameters shown in [Table 10.a](#) will be recorded for urine analysis, hematology, and serum chemistry.

Table 10.a Clinical Hematology, Chemistry, and Urinalysis

Hematology	Chemistry		Urinalysis
Hematocrit	Albumin	Chloride	Glucose
Hemoglobin	ALP	GGT	Nitrite
Platelets	ALT	Glucose	Occult blood
RBC	AST	Magnesium	pH
WBC	Bicarbonate	Potassium	Protein
	BUN	Sodium	Specific gravity
	Calcium	Total bilirubin	
	Creatinine kinase	Total protein	
	Creatinine		

ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, GGT=gamma glutamyl transferase, RBC=red blood cell, WBC=white blood cell

10.2.2.13 Serum Markers of Bone Metabolism

Results of serum markers of bone metabolism (ie, crosslaps, osteocalcin, phosphorus, 25-hydroxy vitamin D) will be recorded.

10.2.2.14 GnRH Stimulation Test

Results of GnRH stimulation tests (concentrations of LH and FSH at 0/30/60/90/120 min after injection) will be recorded.

10.2.2.15 Vaginal Bleeding (Females)

Any data of vaginal bleeding incidence (start/end dates and frequency) will be recorded.

10.2.2.16 Physical Examination

Any data of physical examination (ie, examination of the eyes, ears, nose, throat, cardiovascular system, respiratory system, gastrointestinal system, dermatologic system, extremities, musculoskeletal system, nervous system, lymph nodes, other) will be recorded.

10.2.2.17 ECG

12-lead ECG results (QT interval, corrected QTc interval [QTc], presence of any abnormalities) will be recorded.

10.2.2.18 Date of Visits and/or Hospitalizations

Date of visits and/or hospitalizations to the site will be recorded.

10.2.2.19 Drug Administration for CPP Treatment

The first date and dose of administration of ENANTONE, and the last date and dose of recorded administration of ENANTONE, and any other available data during the Treatment Phase will be

recorded. The dates of the first and last dose of ENANTONE need to be during the index period from 1 September 1998 to 30 September 2018.

If another GnRH agonist, such as generic leuporelin, was administered for the treatment of CPP after 9 months of continuous ENANTONE, the first date and dose of administration of the GnRH agonist, and the last date and dose of recorded administration of the GnRH agonist, the medication name, and any other available data during the GnRH Treatment Intervals will be recorded.

10.2.2.20 Adverse Events

Data on any AEs and SAEs (refer to Section 12.1 for definitions) will be recorded.

10.2.2.21 Study Completion

The reason for the completion of treatment with ENANTONE will be recorded.

10.2.3 Variables Collected During Each Study Phase

All data on the study-related variables described in Section 10.2.2 can be collected as available. Required variables to be collected during each study phase are described in the following Sections 10.2.3.1 and 10.2.3.2.

When the subject meets the protocol's eligibility criteria (inclusion criteria) and henceforth enrolled into the study, the subject's missing data – despite not satisfactory to fulfil a complete analysis for primary and secondary endpoints– will not be regarded as protocol deviation.

10.2.3.1 Variables Collected Prior to ENANTONE Treatment Initiation

- Informed consent
- Patient demographics
- Disease history
- BMD (z-scores)
- Bone age and growth rate
- Height, predicted adult height, and weight
- Medical history and comorbidities
- Prior and concomitant medications
- Evaluation of long term effect on reproduction
 - Menstruation cycles (females)
 - Pelvic measurement
 - Sexual characteristic examination

- Hormonal measurements
 - β -HCG (females)
 - Pregnancy
- Tanner staging
- Cranial CT/MRI
- Clinical laboratory test
- Serum markers of bone metabolism
- GnRH stimulation test
- Physical examination
- Date of visits and/or hospitalizations
- Adverse events

10.2.3.2 Variables Collected During ENANTONE Treatment Phase, Follow-up Phase and GnRHa Treatment Intervals

- Vaginal bleeding (females)
- BMD (z-scores)
- Bone age and growth rate
- Height, predicted adult height and weight
- Medical history and comorbidities
- Prior and concomitant medications
- Evaluation of long term effect on reproduction
 - Menstruation cycles (females)
 - Pelvic measurement
 - Sexual characteristic examination
 - Hormonal measurements
 - β -HCG (females)
 - Pregnancy
- Tanner staging
- Cranial CT/MRI
- Clinical laboratory test

- Serum markers of bone metabolism
- GnRH stimulation test
- Physical examination
- ECG
- Drug administration for CPP treatment (refer to Section 10.2.2.19)
- Adverse events
- Study Completion

10.3 Data Sources

This retrospective study will analyze data from medical records of CPP subjects (from approximately 300 subjects), from multiple centers across China. Approximately 6 medical facilities in China, from both northern and southern region of China will be selected for this study. The medical results of subjects from these medical facilities should provide reliable data on variables during the specified study phases as described in Section 10.2.2 and 10.2.3. The data collected between index period from 1 September 1998 to 30 September 2018 will be analyzed in this study. All data collected from patient's medical chart can be reported as available. Patients from Leuprorelin-4001 Study can also be considered for Leuprorelin-5001 Study, with emphasis placed on analysis of data during the follow-up after the end of treatment with ENANTONE, considering this data will be lacking from these patients in the Leuprorelin-4001 Study.

This study is observational and data will be collected as part of routine clinical practice and the outcomes will be reported based on available data. No imputation of missing data will be conducted.

10.4 Study Population

10.4.1 Inclusion Criteria

- 1) Subjects with diagnosis of idiopathic CPP
- 2) Subjects treated with leuprorelin acetate (ENANTONE) for at least 9 continuous months of therapy with either a stable dose of high dose (≥ 90 $\mu\text{g/kg}$ up to 180 $\mu\text{g/kg}$) or low dose (< 90 $\mu\text{g/kg}$ down to 30 $\mu\text{g/kg}$).
- 3) Subjects initiated and completed treatment during the index period from 1 September 1998 to 30 September 2018
- 4) Subjects who have the following information prior to initiation of ENANTONE and at least one record of each of the following parameters at the end of ENANTONE treatment in the medical records: Tanner staging, estradiol or testosterone level, and FSH and LH level. The subject should have at least one record of bone age prior to the initiation GnRHa therapy

with ENANTONE to support the diagnosis of CPP. In addition, the subject should have at least one record of bone age during treatment with ENANTONE.

- 5) The subject or, when applicable, the subject's legally acceptable representative signs and dates a written informed consent form and any required privacy authorization prior to the initiation of any study procedure

10.4.2 Exclusion criteria

- 1) Subjects treated with leuprorelin acetate or any other GnRHa for conditions other than CPP
- 2) Subjects used any other GnRHa products for CPP treatment prior to initiation of ENANTONE therapy
- 3) CPP patients with identified etiology, such as brain tumor or cranial irradiation

10.5 Study Size

Approximately 300 subjects will be enrolled into the study from multiple centers across China, as required by the CFDA. Within each site, eligible subjects will be enrolled until the site's subject quota has been reached. The above sample size, if evenly split between low dose and high dose, will provide 95% confidence intervals (CIs) for the primary effectiveness variable with margins of error of approximately 7% and 6% if the observed effectiveness rates are 75% and 85%, respectively for low and high doses. Furthermore under these same assumptions a 95% CI for the odds ratio would have a lower bound >1.0 , suggesting greater effectiveness for subjects treated with the high dose.

10.6 Data Handling and Recordkeeping

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, 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).

10.6.1 Case Report Forms (Paper)

Completed case report forms (CRFs) are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with paper CRFs. The sponsor will make arrangements to train appropriate site staff in the use of the CRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. CRFs must be completed in English. All paper CRFs must be filled out legibly in black or blue ballpoint ink (use of black ink is preferred).

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, and missing or unclear data. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections to paper CRFs are to be made by making a single-line strikeout of the incorrect information and writing in the revisions. All corrections must be initialed and dated. Reasons for significant corrections should additionally be included. All new additions are to be made with the date and signature or seal affixed.

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

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

CRFs 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 CRFs. The completed CRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

10.6.2 Record Retention

The investigator agrees to keep the records stipulated in Section 10.6.1 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), copies of all paper CRFs and query responses, 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.

10.7 Data Analysis

The clinical effective therapeutic dose as well as safety and effectiveness data of leuprorelin acetate used for the treatment of CPP will be summarized primarily using descriptive statistics; however inferential methods may be used to provide covariate adjustment as well as an indicator of data strength. To support the study objectives the primary data summaries will be focused on the ENANTONE treatment phase and the follow-up phase. The definition of each of these phases will be developed in the SAP. If more than 5% of subjects have CPP treatment with a generic GnRHa after ENANTONE then complimentary safety summary tables will be presented on those data from that therapy.

10.7.1 Analysis Sets

A statistical analysis plan (SAP) will be developed prior to releasing the study data to statisticians for analysis. Unless otherwise specified, statistical analyses will be performed using SAS © version 9.2, or later. Unless otherwise specified, data analyses and tabulations will be by dose level (high or low) and all subjects combined; with supportive analyses stratified by sex. Additional stratification variables may be identified in the SAP.

All enrolled subjects who are enrolled will be included in the Safety Analysis Set and the Full Analysis Set (FAS).

If 5% or more of the FAS set are found to have violated some of the following study criteria then repeat analysis will be performed on the Per Protocol Set, defined as subjects as follows:

- Duration of treatment of at least 9 continuous months of leuprorelin acetate (ENANTONE), with evaluation

10.7.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for each of the dose level groups (high, low dose). Descriptive statistics (eg, N, mean, standard deviation, median, minimum, and maximum) will be generated for continuous variables (eg, age, height, weight, etc.) and the number and percentage of subjects within each category will be presented for categorical variables (eg, sex). Additional categories (eg, BMI intervals) maybe specified in the SAP. Medical history, concurrent medical conditions and concomitant medications will be tabulated. Descriptive statistics will also be determined for duration of time on treatment and follow up by dose level and by demographic categories (eg, male, female) within dose level.

10.7.3 Effectiveness Analysis

Any inferential statistical analysis resulting in p-values will be reported for the purpose of identifying notable findings rather than any formal test of statistical significance. Unless specified otherwise, all point estimates will be estimated alongside a companion 95% CI.

The primary effectiveness outcome, percentage of subjects who have regression or no progression (ie, response to treatment) in Tanner staging at the end of the ENANTONE Treatment Phase will be analyzed using a Cochran-Mantel-Haenszel (CMH) test with sex as

strata variable and dose (high, low) as independent variable. The adjusted odds ratio and 95% CI will be provided from the CMH test along with two-sided p-value. The 95% CI for the percent will also be determined using Clopper-Pearson exact method, unadjusted for sex, will be provided for overall responder and for each sub-response (regression/ no progression) for all subjects and by sex. If the final data are incompatible with the above analyses, then another method, such as ordinary percentages with 95% CIs (example using Wald type CIs), may be used.

Additional CMH analyses with adjustment by other demographic variables may be performed where necessary. If the data in the treatment period permits, similar analysis as described above will be performed at year intervals from the initiation of treatment, ie, Year 1, Year 2, etc.

The above analyses methodology will be also applied to the following effectiveness outcomes, at the end of the treatment phase and at year intervals, if appropriate:

- Percentage of patients with LH suppression
- Percentage of patients with FSH suppression
- Percentage of patients with estradiol or testosterone level suppression to prepubertal level
- Percentage of patients with a decrease from baseline in the ratio of bone age to chronological age
- Percentage of patients with an increase from baseline in predicted adult height

Change from baseline for BMI at end of treatment phase will be analyzed. This analysis will also be performed at each year interval, as permitted by available data and where applicable, of the treatment phase.

The above analysis will be used for the following quantitative variables, with associated baseline value as covariate:

- Change from baseline in BMI during the follow up phase, at yearly intervals, with end of treatment phase BMI as baseline
- Change from baseline in BMD, at end of treatment phase and at yearly intervals
- Change from baseline in BMD during the follow up phase, at yearly intervals with the end of treatment phase bone density as baseline
- Change from baseline in patient height, at end of treatment phase and at yearly intervals
- Change from baseline in patient height during the follow up phase, at yearly intervals with end of treatment phase height as baseline

10.7.4 Safety Analysis

Safety outcomes will be analyzed by treatment (high, low dose) and overall, and unless specified otherwise, will not be stratified by sex. Separate summaries will be performed for the treatment phase and the follow up phase, both overall and at year intervals.

The primary safety outcome is the incidence per 100 person years (with 95% CIs) of AE and SAEs. All AEs and SAEs will be coded using the MedDRA coding dictionary. AEs and SAEs will be summarized together and separately at both MedDRA levels system organ class (SOC) and preferred term by tabulating the numbers of events, person years at risk and incidence per 100 person years. Furthermore, overall total number of events, person years at risk, and incidence per 100 person years (ie, any AE/SOC at any time) will be provided.

Incidence rates per 100 person years (95% CI) for polycystic ovarian syndrome will be determined for female subjects, by treatment group. Incidence rates per 100 person years for injection site reaction will be determined by treatment group.

If the data permit, changes in standard laboratory tests will be summarized using descriptive statistics.

10.8 Quality Control and Quality Assurance

The study will be conducted in accordance with the International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) (http://www.pharmacoepi.org/resources/guidelines_08027.cfm).

10.8.1 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 CRFs. 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 (contract research organization; CRO) and by the institutional review board (IRB) or independent ethics committee (IEC).

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Binder, 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 CRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

10.8.2 Protocol Deviations

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, 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.

Note that missing data – despite not satisfactory to fulfil a complete analysis for primary and secondary endpoints– will not be regarded as protocol deviation.

10.8.3 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 [PMDA]). 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 [10.8.1](#).

10.9 Limitations of the Research Methods

This is an observational study, where the assignment to the dose level of leuprorelin acetate is at the discretion of the treating physician, which may also vary according to the patient's body mass. Unlike clinical trials where treatment assignment is randomized to reduce physician bias, no randomization is used in the dose selection, and certain biases and confounding influences are inevitably present in the data to be analyzed. Subgroup analysis to evaluate the effect of dose on study outcomes will be performed for selected parameters.

This study is not statistically powered for any hypothesis testing, and all outcomes will be summarized using descriptive statistics. Since this study is observational and data will be collected as part of routine clinical practice and outcomes will be reported on the available data. No imputation of missing data will be conducted.

11.0 PROTECTION OF HUMAN SUBJECTS

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 Good Clinical Practice (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 A](#). The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

11.1 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.

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.

11.2 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.

11.3 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, PMDA), 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 11.2).

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 CRF).

11.4 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results as required by protocol, 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.

12.0 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

12.1 Definitions

Adverse Events

An AE is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, a new disease or worsening in severity or frequency of a concomitant disease, temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Adverse Reactions

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

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 12.a](#)).

Table 12.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
Malignant hypertension	Anaphylactic shock
Convulsive seizure	Acute renal failure
Agranulocytosis	Pulmonary hypertension
Aplastic anemia	Pulmonary fibrosis
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected endotoxin shock
	Confirmed or suspected transmission of infectious agent by a medicinal product
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as “Important Medical Events” satisfying SAE reporting requirements.

12.2 Collection and Recording of Adverse Events

Reports of adverse events/reactions which are study outcomes or study covariates should be summarized as part of any interim safety analysis and in the final study report. SAE/adverse drug reaction (ADR) should be reported according to the following procedure:

A Takeda SAE/ADR 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/related.
- Subject identification number.
- Investigator’s name.
- Name of the study medication(s).
- Causality assessment.

The SAE/ADR form should be transmitted within 24 hours to the attention of the contact listed in Section 4.0. The investigator should make sure the success of the reporting transmission.

12.3 Reporting of Adverse Reactions to Regulatory Authorities/Ethics Committee

Reporting will be in accordance with national regulations in China.

12.4 Other Safety Information

Where any of the following are study outcomes or covariates, they will be summarized in the study report and any interim reports:

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- **Use during pregnancy**
- **Overdose:** This refers to the administration of a quantity of a drug given per administration or cumulatively, which is above the maximum recommended dose according to the authorised product information. Clinical judgement should always be applied.
- **Off-label use:** This relates to situations where the drug is intentionally used for a medical purpose not in accordance with the authorised product information.
- **Misuse:** This refers to situations where the drug is intentionally and inappropriately used not in accordance with the authorised product information.
- **Abuse:** This corresponds to the persistent or sporadic, intentional excessive use of a drug, which is accompanied by harmful physical or psychological effects.
- **Medication error:** This refers to any unintentional error in the prescribing, dispensing, or administration of a drug while in the control of the healthcare professional or patient.
- **Accidental occupational exposure:** This refers to exposure to a drug, as a result of one's professional or non-professional occupation.

13.0 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

It is intended that study results will be presented to CFDA, as part of regulatory commitment study, to justify leuprorelin acetate long term use in China. Publication in peer-reviewed journals and presentation at scientific conferences may also be considered.

14.0 REFERENCES

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- [8] Lee PA, Klein K, Mauras N, Neely EK, Bloch CA, Larsen L, et al. Efficacy and safety of leuprolide acetate 3-month depot 11.25 milligrams or 30 milligrams for the treatment of central precocious puberty. *J Clin Endocrinol Metab*. 2012;97(5):1572-80.

15.0 APPENDICES

Annex 1 List of Stand-Alone Documents

Number	Document Reference Number	Date	Title
1	Appendix A	NA	Responsibilities of the Investigator
2	Appendix B	NA	Investigator Consent to Use of Personal Information

Appendix A 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 CRFs, 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. Report adverse reactions to the sponsor promptly.

Appendix B 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

Amendment 1 to An Observational, Retrospective Study to Evaluate the Long Term Safety and Effectiveness of
Leuporelin in the Treatment of Central Precocious Puberty

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Pharmacovigilance Approval	29-Jan-2018 13:33 UTC
	Biostatistics Approval	29-Jan-2018 14:03 UTC
	Clinical Science Approval	29-Jan-2018 19:23 UTC