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

NCT Number: NCT02427958

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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

Statistical Analysis Plan

Version: 1.0

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SPONSOR APPROVAL PAGE

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Statistical Analysis Plan

Version: 1.0

Prepared by:

PPD

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ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AFP	alpha-fetoprotein
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-HCG	beta human chorionic gonadotropin
BA	bone age
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
IRB	institutional review board
LFT	liver function test
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
PPS	per protocol analysis set
PT	preferred term
PTE	pretreatment event
QTc	corrected QT interval
SAE	serious adverse event

Abbreviation	Definition
SAP	statistical analysis plan
SC	subcutaneous
SS	safety analysis set
SOC	system organ class
TEAE	treatment-emergent adverse event
TW3	Tanner-Whitehouse 3
ULN	upper limit of normal
WHODRUG	World Health Organization Drug Dictionary

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives for Protocol Leuprorelin-4001.

All decisions regarding final analysis, as defined in this SAP document, have been made prior to Database Lock (DBL) of the study data.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

To evaluate the safety of leuprorelin in subjects with central precocious puberty (CPP).

2.1.2. Secondary Objective

To evaluate the efficacy of leuprorelin in subjects with CPP.

2.2. Endpoints

2.2.1. Primary Endpoint

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

2.2.2. Secondary Endpoint

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

2.2.3. Additional Endpoints

- Percentage of subjects with suppression of peak luteinizing hormone (LH) and follicle-stimulating hormone (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 bone age (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.

3. 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.
- Eligible CPP subjects with body weight <20 kg will receive recommended dose of 1.88 mg SC every 4 weeks.

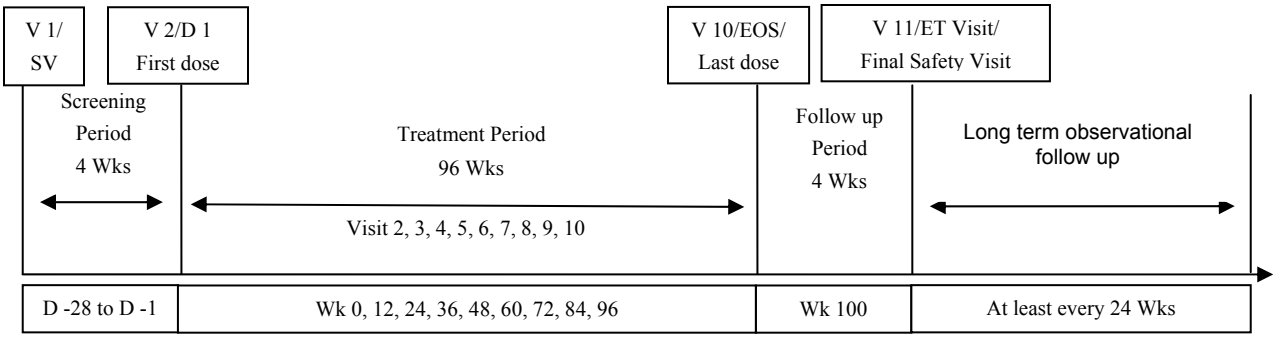
It is not recommended to exceed 180 μg/kg. The dose can be adjusted based on subject's condition and investigator's judgment. Study visits, procedures, and evaluation are summarized in the Schedule of Study Procedures (Appendix A). Subjects will be followed until the end of the study, during which time 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.

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 [1]. 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 3.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**Error! Reference source not found.**.

4. SAMPLE SIZE CONSIDERATION

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).

5. ANALYSIS SETS

- Safety Analysis Set (SS): The SS consists of all subjects who are enrolled and received at least 1 dose of study drug.

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

- Per Protocol Analysis Set (PPS): The PPS consists of all subjects who are in the FAS and have none of the following major protocol violations:
    - Subject doesn't complete the Week 96 visit;
    - Subject has less than 90% treatment compliance;
    - Subject fails to meet inclusion criteria No.s: 3, 4 and 6;
    - Subject meets exclusion criteria No.s: 1, 2, 4, 5, 6, and 8.

6. STATISTICAL ANALYSIS

6.1. General Statistical Considerations

Statistical analysis will be performed using SAS® software (SAS Institute, Inc., Cary, North Carolina) Version 9.2, or later.

Unless otherswise specified, all data summaries will be performed for the following groups: Males, Females, and All Subjects. Also, where applicable, separate tables will be provided for the Treatment period (upto including Week 100 visit) and the Follow-up period. Continuous variables will be summarized including the number, the mean, the standard deviation, median, minimum and maximum. Categorical variables will be summarized including the number and percentage of subjects.

6.2. Data Handling Conventions

6.2.1. Premature Withdrawal and Missing Data

No imputation will be used for Missing data.

6.2.2. Definition of Baseline and Change from Baseline

Baseline is defined as the last non-missing measurement prior to first dose of study drug.

The change from baseline will be calculated by subtracting the baseline values from the individual post-baseline values. If either the baseline or post-baseline value is missing, the change from baseline is set to missing as well.

6.2.3. Definition of Study Day

For Screening and Treatment periods, the study day number will be calculated with respect to the treatment start date, and for the Follow-up period it will be calculated with respect to the date of the Week 100 Visit. Study Day is missing when target date is missing, and it is equal to target date – reference date when target date less than reference date, and it is equal to target date – reference date+1

when target date equal to or more than reference date. Therefore the day of first investigational drug administration for Treatment period is Day 1 and the day before first investigational drug administration for Treatment period is Day -1. The windows for mapping study days to study visit, for anlaysis purposes, is listed as table 6.a.Table 6.a Mapping study days to study visit

Period	Week/Study Day	Visit Windows(Day)	Visit Number
Screening	Day -28 to -1	NA	1
Treatment	Week 0/Day 1	NA	2
	Week 12/Day 84	±14d	3
	Week 24/Day 168	±14d	4
	Week 36/Day 252	±14d	5
	Week 48/Day 336	±14d	6
	Week 60/Day 420	±14d	7
	Week 72/Day 504	±14d	8
	Week 84/Day 588	±14d	9
	Week 96/Day 672	±14d	10
Final safety Visit/ Early Termination Visit	Week 100/Day 700	±14d	11
Follow up	At 24 week intervals	±28d	

6.3. Study Subjects

6.3.1. Disposition of Subjects

The number and percentage of subjects, that complete the study, or prematurely withdraw from the study will be summarized using safety analysis set. The number and percentage of subject that complete the treatment phase will also be tallied as well as the disposition of the subjects that discontinued prior to the follow-up period. In addition, the number and percentage of subjects who discontinuation from the study will be summarized by primary reason. In addition, individual reasons for discontinuation will be listed.

The following category for primary discontinuation reason will be presented for this study.

- Pretreatment Event (PTE) or AE
- Significant Protocol Deviation
- Lost to Follow-up

- Voluntary Withdrawal
- Study Termination
- Pregnancy
- Lack of Efficacy
- Investigator Judgment
- Screen Failure
- Other

6.3.2. Protocol Deviation

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 institutional review board [IRB] or ethics committee [EC], as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

The following category for deviation will be presented for this study.

- Entry Criteria
- Concomitant Medication
- Procedure Not Performed per protocol (Primary Endpoint or Safety Related)
- Study Medication
- Withdrawal Criteria
- Specify Deviation (Description, include date of site awareness if relevant)

A summary of the number and percentage of patients with an significant protocol deviation by type of deviation will be provided using safety analysis set. Individual subject listings of significant protocol deviations will be provided.

6.3.3. Demographic and Baseline Characteristics

Patient demographics will be summarized using the safety analysis set.. The following demographic information will be presented for this study:

- Sex;
- Age;
- Race;

- Height
- Weight (as continuous variable)
- Weight categories (i.e. <20 kg, ≥20 kg)
- Age at date of diagnosis of CPP (derived determining number of days between date of birth and date of diagnosis divided by 365.25 to obtain age in years).

Patient baseline characteristics will be summarized using the safety analysis set. The following baseline characteristics information will be presented for this study:

- Tanner staging evaluation;
- LH and FSH;
- Estradiol or Testosterone;
- Predicted adult height;
- Bone age;
- BMI;
- Bone mineral density;

Individual subject demographic and baseline characteristics data will be listed.

6.3.4. Medical History and Concurrent medical conditions

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.

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.

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.

Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and will be tabulated for the number and percent of patients by decreasing frequency based on safety analysis set..

Individual medical history and concurrent medical conditions data will be listed.

6.3.5. Concomitant Medications

Medication start and stop dates will be compared to the date of first dose of treatment to be classified as prior medications and concomitant medications.

Prior medications are those medications that start and stop prior to the date of first dose of study treatment. Concomitant medications is any drug given in addition to the study medication and defines as those medications that start before, on or after the first day of study treatment of the defined treatment period and continue into the treatment period and/or continue into 30 days after last dose or after the week 100 visit.

Concomitant therapy will be classified according to the World Health Organization Drug Dictionary (WHODRUG) and tabulated by WHO drug Anatomical Therapeutic Chemical (ATC) classification sorted by decreasing frequency and dose level based on safety analysis set.

Individual subject concomitant medication data will be listed.

6.4. Efficacy Analyses

Efficacy analyses will be summarized using the FAS analysis set. Unless otherwise specified each summary of the efficacy variables will be presented for the primary time point (Week 96) as well as each planned visit. Only observed data will be summarized, and missing data will not be imputed. However, a visit called Final Visit will also be summarized; Final Value is defined as the last treatment phase value (ie. post-baseline and ≤ Week 100).

A Pre-pubertal level will be any value less than (<) the upper limit of normal for the local laboratory, which value may be dependent on sex and/or age. If laboratory values are coverted to a common unit the normal ranges should also converted, however all comparisons to the pre-pudertal level should be performed on the original unit.

The related variables for efficacy analyses will be presented for this study.

- Tanner staging
- peak LH and FSH
- basal estradiol (female) or testosterone level (male)
- predicted adult height
- the ratio of bone age to chronological age

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, i.e. simultaneously, after stimulation to pre-pubertal level at Week 96 (Visit 10) will be summarized, individual data will be listed. For each subject at each visit the peak value (i.e. largest value of the 0, 30, 60, 90 min samples) from the stimulation tests will be used,

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 (Visit 10) will be summarized, individual data will be listed.

The number and percentage of subjects with improvement in predicted adult height at Week 96 (Visit 10) 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 (Visit 10) compared with Baseline will be summarized, individual data will be listed. Chronological age is determined using birthdate and date of the procedure to obtain age in days and then deviding by 365.25 to obtain age in years, not truncated to an integer.

For above binary data, 95% confidence intervals will be presented with exact (Clopper-Pearson) method.

6.5. Safety Analyses

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.

6.5.1. Adverse Events

Adverse events, including SAEs, are recorded in the eCRFs. AEs observed during the treatment period will be classified as treatment emergent adverse events (TEAEs) while those recorded during the follow-up period will be classified as clinical events. Each AE will be coded to system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

TEAEs are defined as AEs with onset occurring during the treatment phase and/or within 30 days (onset date – last date of dose +1≤ 30) after last study drug administration. However, for subjects that continue into the follow-up period, TEAEs will include all AEs up to the Week 100 visit. Clinical events will be any AE with onset after the Week 100 visit.

In general, AEs may be analyzed one of two ways. First method (subject count) is to report the count and percent of subjects reporting the AE. In this analysis a subject is only counted 1 time for the specific AE, and the percentage is with respect to the number of subjects in that safety set. For the treatment period the safety set is all subjects who receive at least 1 dose of study drug. For the follow-up period the safety set will be all subjects with at least 1 follow-up visit after the Week 100 visit. Second method (event count) is to count all events, for the specific AE, and calculate the rate per 100 patient years. Patient years (no. of days/365.25) for the treatment period will be determined from Day 1 to date of the Week 100 visit; patient years in follow-up period will be determined, at the subject level, from date of the Week 100 visit to date of last contact.

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. Lead to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   a. May require intervention to prevent items 1 through 5 above.
   b. May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   c. Includes any event or synonym described in the Takeda Medically Significant AE List (Table 6.b).

Table 6.b Takeda Medically Significant AE List

Term	
Acute respiratory failure/Acute respiratory distress syndrome (ARDS)	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 anaemia	Pulmonary fibrosis
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected endotoxin shock
	Confirmed or suspected transmission of infection agent by a medicinal product
	Neuroleptic malignant syndrome/malignant hyperthermia
	Spontaneous abortion/stillbirth and fetal death

A PTE is defined as any untoward medical experience which occurs in a subject who has signed an informed consent to participate in the study but prior to the administration of any study medication; it does not necessarily have to have a causal relationship with study medication or study procedures.

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, 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. In addition, an abnormal Liver Function Tests (LFT) Increases eCRF must be completed.

For each study period AEs will be analyzed using the subject count method and the event count method, as described above. In each AE summary table, AEs will be presented at the MedDRA PT and SOC level. In these tables SOC levels will be listed alphabetically and under each SOC the PTs will be listed in order of decreasing frequency. Below is a list of different AE classifications to be analyzed; additional classifications may be identified later. Where appropriate, similar analyses will be produced for clinical events (i.e. those events reported during the follow up period).

- all TEAEs
- SAEs

  - Repeat this analysis using all AE results for both the treatment phase and follow up phase pooled together.

- Non serious AEs only at the PT level, overall and only those AEs meeting a minimum rate (eg. 5%)
  - Repeat this analysis using all AE results for both the treatment phase and follow up phase pooled together.
- drug-related TEAEs
- relationship of TEAEs to study drug (related vs. not-related)
- severity of TEAEs (Mild, Moderate, Severe)
- polycystic ovarian syndrome in female subjects

Data listings will be provided for all AEs including PTE, TEAEs, AEs leading to study drug discontinuation, and SAEs.

6.5.2. 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 at each scheduled visit (Table 6.c).

All clinical laboratory data (Table 6.c) will be listed.

Table 6.c Safety laboratory test

Laboratory Test	Sample	Visit
Hematology	RBC WBC Hemoglobin Hematocrit Platelets	Visit1, 4, 6, 8, 11 Follow-up visit Unscheduled Visit
Clinical Chemistry	ALT Albumin Alkaline phosphatase AST Total bilirubin Total protein Creatinine	Visit1, 4, 6, 8, 11 Follow-up visit Unscheduled Visit

	Blood urea nitrogen Creatine kinase GGT Potassium Sodium Glucose Chloride Bicarbonate Calcium Magnesium	
Urinalysis	pH Protein Glucose Blood Nitrite Microscopic Analysis (only if positive dipstick results): RBC/high power field WBC/high power field Epithelial cells, casts etc	Visit1, 6, 11 Unscheduled Visit

6.5.3. Vital Signs

Vital signs include body temperature, respiratory rate, systolic blood pressure, diastolic blood pressure and pulse at each visit including scheduled visit (visit 1, 2, 3, 4, 5, 6, 7 8, 9, 10, 11, follow-up visit) and unscheduled visit.

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 at each scheduled visit.

All vital sign data will be provided in the data listings.

6.5.4. Height, Weight and BMI

Baseline, postdose, and changes from Baseline in height, weight and BMI measurements will be summarize at each scheduled visit.

All data for height, weight, BMI will be provided in the data listings.

6.5.5. ECG

A standard 12-lead ECG will be recorded at each scheduled visit (visit 1, 3, 5, 7, 10, follow-up visit) and unscheduled visit. The investigator (or a qualified observer at the investigational site) will interpret the ECG within normal limits (Normal), abnormal but not clinically significant (Abnormal, NCS), or abnormal and clinically significant (Abnormal, CS).

Individual results of quantitative ECG parameters from the 12-lead safety ECGs that meet TDC's markedly abnormal criteria will be summarized and listed. Analysis of central tendency for QT/corrected QT interval (QTc) and categorical analysis of QT/QTc will be performed.

Baseline, postdose, and changes from Baseline for QT/corrected QT interval (QTc) will be summarized at each scheduled visit (visit 1, 3, 5, 7, 10, follow-up visit).

Shift tables will be generated for the investigator's ECG interpretations(Normal, Abnormal and NCS, Abnormal and CS) that changed from Baseline to the postdose collections by above groups at each scheduled visit (visit 1, 3, 5, 7, 10, follow-up visit).

All ECG data will be provided in the data listings.

6.6. Other Analyses

The serum bone metabolism biomarkers including phosphorus, 25-hydroxy vitamin D, osteocalcin, crosslaps will be summarized at each scheduled visit (visit 2, 11) 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 at each scheduled visit (visit 2, 11). All bone mineral density data will be provided in the data listings.

Pelvic and testicular ultrasonography will be summarized at each scheduled visit (visit 1, 4, 6, 8, 10, 11, follow-up visit) and data will be provided in listings.

Other Variables:

The physical examination findings will be presented in data listings.

The urine pregnancy test, cranial magnetic resonance imaging (MRI), carcino-embryonic antigen (CEA), alpha-fetoprotein (AFP) and beta human chorionic gonadotropin (β-HCG) at Screening will be summarized and listed.

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

6.7. Interim Analyses

One interim analysis will be performed after Week 100(visit 11). 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.

7. REFERENCES

1. CAI Depei, Precocious puberty and pubertal delay; Shanghai, China: Fudan University Press; June 1 2003, 16-23.

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 **Error! Reference source not found.**. 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) F 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).