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

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Leuprorelin-5001

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

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1.1 Approval Signatures

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

Approvals:

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3.0 LIST OF ABBREVIATIONS

AE	adverse event
ADR	adverse drug reaction
ATC	Anatomical Therapeutic Chemical
BA	bone age
BMD	Bone Mineral Density
BMI	body mass index
CA	chronological age
CPK	creatine phosphokinase
CFDA	China Food and Drug Administration
CI	Confidence Interval
CM	Concomitant Medications
CPP	central precocious puberty
CRF	case report form
CRO	contract research organization
CT	computed tomography
DBL	Database Lock
EC	ethics committee
ECG	electrocardiogram
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GnRH	gonadotropin releasing hormone
GnRHa	gonadotropin releasing hormone analogs
IRB	institutional review board
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MH	Medication History
PPS	per protocol analysis set
PT	preferred term
PUB	Post-Puberty
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SS	safety analysis set
SOC	system organ class
WHO	World Health Organization
WHODRUG	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objectives

The goal of this study is to evaluate the safety and effectiveness of leuprorelin acetate in central precocious puberty (CPP) treatment in China.

Objective 1: To evaluate the safety of high dose leuprorelin acetate (≥ 90 μg/kg up to 180 μg/kg) and low dose leuprorelin acetate (< 90 μg/kg down to 30 μg/kg) in CPP treatment of at least 9 continuous months of ENANTONE

Objective 2: To evaluate the long-term effectiveness of high dose leuprorelin acetate (≥ 90 μg/kg up to 180 μg/kg) and low dose leuprorelin acetate (< 90 μg/kg down to 30 μg/kg) in CPP treatment of at least 9 continuous months of ENANTONE

4.2 Secondary Objectives

Not applicable.

4.3 Additional Objectives

Not applicable.

4.4 Study Design

This observational retrospective study will evaluate the long-term safety and effectiveness of ENANTONE (leuprorelin acetate) for the treatment of CPP.

The procotol was written to include approximately 300 patients with CPP, treated with ENANTONE for at least 9 continuous months, and who initiated and received the last dose of treatment during the index period (from 1 September 1998 to 30 September 2018). With the approval of China's Center for Drug Evaluation the study was then modified to collect information from only 100 subjects. Patients who were treated with other GnRHa (including generic leuprorelin acetate) after the 9-month treatment with ENANTONE could be enrolled into the study. At each clinical site, sequential eligible patients were to be enrolled until the site's patient quota has been reached. Medical records of enrolled patients were collected and reviewed.

Study participants were expected to have met inclusion criteria, including the following key items:

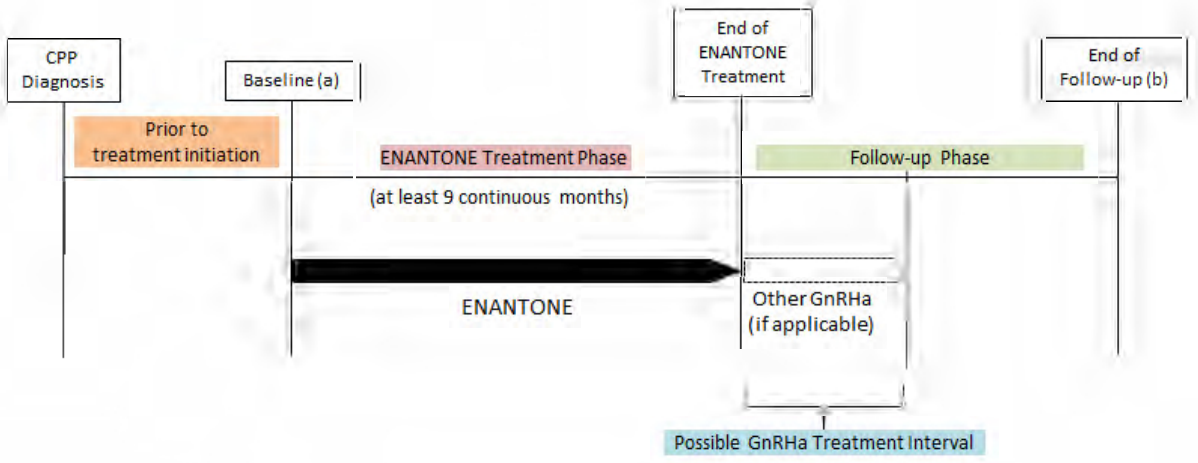
- Subjects with diagnosis of idiopathic CPP
- Subjects treated with leuprorelin acetate (ENANTONE) for at least 9 continuous months of therapy with either a stable dose of high dose (≥90 μg/kg up to 180 μg/kg) or low dose (<90 μg/kg down to 30 μg/kg).
- Subjects initiated and completed treatment during the index period from 1 September 1998 to 30 September 2018

- 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 of 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.

Prior to ENANTONE treatment initiation, all relevant data (specified in Protocol Section 10.2.3.1), including data pertaining to the diagnosis of CPP will be collected at all available time points. Baseline values were defined as the measurement(s) just prior to the initiation of ENANTONE treatment.

The study design is shown in Figure 4.a. Participants are expected to have data for Baseline (including CPP diagnosis and pre-ENANTONE treatment) phase, the ENANTONE treatment phase (at least 9 continuous months) and Follow-up phase (of variable duration depending upon the duration of available observations). During follow-up phase patients may have been treated with another GnRH after treatment with ENANTONE until discontinuing CPP therapy and allowed to progress to puberty or may have completed their treatment for CPP with ENANTONE and then progress to puberty.

Figure 4.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.

Prior to ENANTONE treatment initiation, all relevant data (specified in Protocol 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 Protocol Section 10.2.2) 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 Protocol Section 10.2.2) 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 GnRHa Treatment Interval may apply to those patients who were treated with a GnRHa (either generic leuprorelin acetate or another GnRHa) after completing the minimum of 9 months therapy with ENANTONE for CPP; in this case, the dates of therapy with this other GnRHa should be noted in the case report form (CRF).

5.0 ANALYSIS OUTCOMES

5.1 Primary Outcome

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

5.2 Secondary Outcome

1. LH and FSH suppression to prepubertal level during and after treatment 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

5.3 Additional Outcome

- Increase in predicted adult height during and after treatment with ENANTONE
- Change from baseline in standard laboratory tests during and after treatment with ENANTONE
- Incidence of polycystic ovarian syndrome during and after treatment with ENANTONE
- Evaluation of long term effect on reproduction
    - Menstruation cycles (females)
    - Pelvic measurement
    - Sexual characteristic examination
    - Hormonal measurements
    - β-HCG (females)
    - Pregnancy
- Change from baseline in bone mineral density (BMD) during and after treatment with ENANTONE.
- Change from baseline in body mass index (BMI) during and after treatment with ENANTONE.

6.0 DETERMINATION OF SAMPLE SIZE

This retrospective study will analyze data from medical records of CPP subjects (from approximately 100 subjects), from multiple centers across China. Eight medical facilities in China, from both northern and southern region of China will be selected for this study. Within each site, eligible subjects will be enrolled until the site's subject quota has been reached. 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.. The protocol sample size, 300 has been revised to 100 subjects following review and approval of China's Center for Drug Evaluation (CDE).

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

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

Data will be associated and summarized by the following:

- ENANTONE treatment phase includes all data from the first dose of ENANTONE up to and including either 45 days, inclusive, after the last dose or date of first dose of a non-ENTANTONE GnRH agonist therapy (earliest case scenario)
- Follow-up phase includes all data after the above defined ENANTONE treatment phase. If the subject continued treatment for CPP with another GnRH agonist after ENANTONE, their data from the follow-up period will be reported separately from those who only received ENANTONE for the treatment of CPP.

Unless specified otherwise, all data summaries will be performed for the following groups: Male, Female and Total, and will be presented during the ENANTONE treatment phase and results during the follow-up phase. 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.

Confidence intervals will be reported as 2-sided 95%, unless otherwise stated.

Means and medians will be presented to 1 more decimal place than the recorded data and standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate. Derived variables may exhibit excessive decimal precision therefore, derived variables may be rounded to a precision representative of the expected data and means, SD and individual values will be formatted in a similar manner as described above.

7.1.1 Study Definitions of Baseline and Change from Baseline

Baseline, for the ENANTONE period, is defined as the last non-missing measurement prior to the first dose of ENANTONE treatment. Unless specified otherwise, baseline values for variables related to CPP will be limited to values collected no more than 3 months (93 days), inclusive, prior to the first dose of ENANTONE.

The change from baseline will be calculated for the treatment period 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 be missing as well.

Data from the follow-up period after completion of treatment period, will be analyzed separately and the baseline for the follow-up period will be defined as the first non-missing measurement after the last dose of GnRHa treatment (with either ENANTONE or another GnRHa).

7.1.2 Definition of Study Days

Study Day 1 is defined as the date on which a subject is administered their first dose of ENANTONE. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

7.1.3 Definition of Study Visit Windows

Unless otherwise specified, longitudinal data will be summarized at 3-month intervals, as indicated in Table 1 below. The Months defined below will be applied to both the ENANTONE and follow-up periods. If actual data exceed the limits as defined by Table 1 then the sequence will be carried forward to satisfy the actual data.

Table 1 Windowing for longitudinal data

Month	Target Study Day	Lower (Day)	Upper (Day)
3	91	46	135
6	182	136	225
9	273	226	315
12	365	316	405
15	456	406	495
18	547	496	585
21	638	586	675
24	730	676	765
27	821	766	855
30	912	856	945
33	1003	946	1035
36	1095	1036	1125
39	1186	1126	1215
42	1277	1216	1305
45	1368	1306	1395
48	1460	1396	1485
51	1551	1486	1575
54	1642	1576	1665
57	1733	1666	1755
60	1825	1756	1845

When a subject has multiple usable records within a window then the record nearest the target day will be used, and when two are equal distant from the target day, different days, then the later will be used. Lastly, if multiple values are on the same day then mean value (if numeric data) or the mode (if categorical data) will be used.

7.1.4 Conventions for Incomplete or Missing date of ENANTONE Therapy

The date of the first ENANTONE administration is necessary for establishing the chronology of all subject data. Likewise, the date for the last administration of ENANTONE has similar importance for indexing subject data. If the month and year are available but the day of administration is missing, an imputed date will be used in the derived data. The imputed day will be in the middle of the month with a date of the 15th of that month chosen as the imputed date. The imputed values will be documented in the data listings alongside the actual recorded date. Because dose scheme may be complicated, based on clinical judgement, other unpredicted special cases will be handled in program with notes documented in the original SAS programs.

7.1.5 Conventions for Missing Adverse Event Dates

Partial dates will be presented as recorded in the listings. Missing and partial AE start dates will be imputed only to determine the relationship between the start date of the event and the first dose date of ENANTONE. The following methods will be used to impute missing or partial dates of AE start dates and end date:

- AE start date month/year available and day missing:
    - If the month and year are the same as those in the first dose date, then first dose date is to be used to impute the AE start date.
    - If the month and/or year are different from those in the first dose date, then first day of the month will be used for the start date.

- AE start date year available and month/day missing:
    - If the year is the same as the year of the first dose, then first dose date is to be used to impute the AE start date.
    - If the year is not the same as the year of the first dose date, set the start date as January 1.

- AE start date completely missing:
    - The first dose date is to be used to impute the AE start date.

7.1.6 Conventions for Missing Concomitant Medication / Medical History Dates

Missing or partial start dates for concomitant medications (CM) / medial history (MH) will be imputed similarly to the strategy given in section 7.1.5.

For end dates for concomitant medications, the following methods will be used to impute missing or partial dates:

- CM/MH end date month/year available and day missing:
    - The last day of month is to be used to impute the end date.

- CM/MH end date year available and month/day missing:
    - The December 31 is to be used to impute the end date.

- CM/MH end date completely missing:
    - The last visit date is to be used to impute the end date.

Note: The imputed date will not be beyond the patient's last visit date.

7.1.7 Conventions for Missing Other Analysis Dates

In order to derive 3-month intervals for efficacy or safety analysis, the following methods can be used to impute missing or partial start dates:

- Start date month/year available and day missing:
  - If the month and year are the same as those in the first dose date of ENANTONE treatment or study day -93, then the first dose date or study day -93 is to be used to impute the start date.
  - If the month and/or year are different from those in the first dose date of ENANTONE treatment or study day -93, then first day of the month will be used for the start date.

- Start date year available and month/day missing:
  - If the year is the same as those in the first dose date of ENANTONE treatment or study day -93, then the first dose date or study day -93 is to be used to impute the start date.
  - If the year is not the same as the year of the first dose date of ENANTONE treatment or study day -93, set the start date as January 1.

7.2 Analysis Sets

- Safety Analysis Set (SS): The SS consists of all enrolled subjects.
- Full Analysis Set (FAS): The FAS consists of all enrolled subjects.
- Per Protocol Analysis Set (PPS): The PPS consists of all subjects who are in the FAS and have no major protocol deviations. If 5% or more of the FAS set are found to have violated some of the study criteria then repeat analysis will be performed on the Per Protocol Set.

7.3 Disposition of Subjects

The number and percentage of subjects, that complete ENANTONE therapy will be tabulated. Otherwise the reasons for not completing ENANTONE therapy will be tabulated. Subjects receiving other GnRHa therapies will be tabulated, and these other therapies will be tabulated, if possible.

The number and percentage of subjects as shown below will also be tabulated.

- Number of subjects
  - Total number of subjects in the ENANTONE treatment period
- Number and percentage of subjects in the follow-up phase after completing treatment with ENANTONE
  - Percentage who had been treated with only ENANTONE
  - Percentage who had been treated with ENANTONE in the treatment phase and then another GnRHa in the follow-up period
- Number and percentage of subjects who completed puberty in the follow-up phase

Puberty is defined as having a Tanner Stage = V after completion of GnRHa therapy with either ENANTONE only or ENANTONE followed by another GnRHa after ENANTONE

The following categories for the reason of primary discontinuation of ENANTONE therapy will be presented for this study.

- Lack of efficacy
- Adverse Event
- Change CPP therapy to another GnRH agonist
- Investigator Judgment
- Other

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

7.4 Demographic and Other Baseline Characteristics

Patient demographics will be summarized using descriptive statistics on the safety analysis set. Individual subject demographics will be listed.

- 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).
- Age of appearance of secondary sexual characteristics
- Age at start of ENANTONE therapy
- Gender
- Family Origin from Northern or Southern China
- Height
- Weight
- BMI

The following baseline information prior to the initiation of ENANTONE therapy will be presented for this study as included in the analysis of the Change from Baseline in these parameters during the ENANTONE treatment period.

- Tanner Stage
- Random LH
- Random FSH
- LH and FSH for each time point during a GnRH stimulation test
- Peak LH during a GnRH stimulation test
- Peak FSH during a GnRH stimulation test

- Estradiol
- Testosterone
- Bone age
- Bone age/chronological age

  The Bone age to Chronological age ratio is determined using birthdate and date of the bone age assessment to obtain age in days and then divided by 365.25 to obtain age in years, not truncated to an integer. Individual chronological age values will be reported to 1 decimal and mean values to 2 decimal places.
- Predicted Adult Height

- Bone Mineral Density (BMD)
- Linear growth rate
- Cranial CT or MRI

7.5 Medical History and Concurrent Medical Conditions

Medical history includes clinically significant diseases and surgeries. Conditions ongoing at the time of ENANTONE treatment are considered concurrent medical conditions.

Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 21.0), and will be tabulated based on safety analysis set. And system organ class (SOC) terms will be sorted by alphabetical order and preferred terms will be sorted in decreasing frequency based on the total number of all subjects.

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

7.6 Medication History and Concomitant Medications

Medication start and stop dates will be compared to the date of first dose of ENANTONE and will be classified as medications taken prior to, concomitant with and concomitant after ENANTONE.

Prior medications are those medications that start and stop prior to the date of first dose of study treatment. Concomitant medication with ENANTONE is any drug given in addition to the study medication, ENANTONE, and defined as those medications that are given on or after the first day of study treatment during the ENANTONE treatment phase. Medication given after ENANTONE is defined as those medications that are given on or after the last dose of ENANTONE and during the follow-up phase. Medications will be classified according to the World Health Organization Drug Dictionary (WHODRUG) and tabulated by WHO drug Anatomical Therapeutic Chemical (ATC) classification based on the safety analysis set. ATC will be sorted using alphabetical order and preferred medication names will be sorted by decreasing frequency based on the total number of all subjects.

Individual subject medication history and medication data will be listed.

7.7 Study Drug Exposure

The following duration of study observations will be summarized (definitions for each are provided later).

- Duration of study observations
  - Duration of observations of CPP diagnosis to end of follow-up period
  - Duration of from 1st dose of ENANTONE to end of treatment period

Similarly, the following duration of the follow-up period will be summarized.

- Duration of the follow-up period for all subjects
- Duration of the follow-up period from last dose of ENANTONE to end of follow-up period for patients who received ENANTONE treatment only
- Duration from start of other GnRHa therapy from 1st dose of GnRHa to the end of the GnRHa treatment
- Duration of the follow-up period for those who were treated with another GnRH agonist during this period, from the last dose of GnRHa to the end of follow-up period, if patient receive another GnRHa

Duration of ENANTONE treatment (defined as time since first administration of ENANTONE treatment in months) will be summarized for the ENANTONE treatment phase. The duration of ENANTONE treatment will be calculated as:

> *(Date of 45 days, inclusive, after the last administration* of *ENANTONE or date of first dose of a non-ENTANTONE GnRHa therapy – Date of first administration of ENANTONE. + 1)/30.44*

Duration of Non-ENANTONE GnRHa treatment (defined from the first dose of a non-ENTANTONE GnRHa therapy to the last dose of any GnRHa other than ENANTONE, even if the treatment changes.) will be summarized, if possible, in Non-ENANTONE follow-up phase:

> *(Date of last administration of any GnRHa other than ENANTONE –. Date of the first administration* of *a non-ENTANTONE GnRHa therapy + 1)/30.44*

Descriptive statistics will be determined for duration of time during the ENANTONE Treatment phase while on ENANTONE treatment, and the duration of time during the follow-up Phase while on other CPP treatment (if applicable) and the duration of follow-up interval after completion of GnRHa therapy for CPP by sex group.

Time Interval of duration of ENANTONE treatment will be tabulated by sex group during the ENANTONE treatment phase for the following time intervals:

- ≥9 months, ≥12 months, ≥18 months, ≥24 months, ≥30 months, ≥36 months, ≥42 months, ≥48 months, ≥54 months, ≥60 months, etc.

The days on ENANTONE treatment is the number of days between first and last ENANTONE injection plus 45 days unless the subject had been on GnRHa in which case this is not 45 days but is the date when they received the 1st dose of the GnRHa. Descriptive statistics of days will be displayed by sex group during the ENANTONE treatment phase.

A by-subject listing of duration of ENANTONE treatment, other CPP treatment during the follow-up interval, duration of follow-up interval after completion of GnRHa therapy for CPP will be provided.

No inferential analysis for comparison duration between sex group will be performed.

7.8 Efficacy Analysis

Efficacy analyses will be performed on the FAS analysis set, and individual data will be listed.

Unless specified otherwise, only 95% confidence interval (CI) will be presented within sex group. No inferential analysis for comparison between sex group will be performed.

As described in section 7.1, efficacy results will be presented separately in the following segments by sex group (male and female plus total):

- Treatment Phase: ENANTONE treatment
- Follow-up Phase:
    - participants that received ENANTONE treatment in the treatment phase
    - If data permit, data from non-ENANTONE GnRHa treatment; as well as data after completion of non-ENANTONE GnRHa treatment

7.8.1 Primary Efficacy Endpoint(s)

The primary effectiveness outcome, percentage of subjects who have regression or no progression (i.e. response to treatment) in Tanner staging at the end of ENANTONE treatment (i.e. the last observation in the ENANTONE treatment phase) will be analyzed using an exact method. The 95% CI for the regression or no progression responder will be determined using Clopper-Pearson exact method. Similar analysis as described above will be performed at 3-month intervals from the initiation of ENANTONE treatment. Additional time intervals maybe utilized as fitting the data.

A Tanner Stage of 5 is satisfied when both evaluations for Tanner scoring are V; specifically, breast development and pubic hair for females and genital development and pubic hair for males.

Where applicable, similar summaries, using the appropriate baseline, will be presented for the follow-up phase at 3-month intervals.

7.8.2 Secondary Efficacy Endpoint(s)

The above analyses methodology and segmented summaries will be also applied to the following efficacy outcomes, at the end of the ENANTONE treatment and evaluated over time using the estimated study visits at 3-month intervals:

- Percentage of patients with peak LH suppression
- Percentage of patients with peak FSH suppression
- Percentage of patients with estradiol or testosterone level suppression to pre pubertal level
- Percentage of patients with a decrease from baseline in the ratio of bone age to chronological age only during treatment with ENANTONE

For each time point, a subject's peak LH (or FSH) value will be determined as largest value of the 0, 30, 60, 90 min samples from the stimulation test.

The abnormal values for a normal pediatric patient population in China for estradiol, testosterone, LH and FSH are listed in Table 2 below.

Table 2 Criteria for Abnormal Values for Estradiol, Testosterone, LH and FSH

Parameter	Unit	Gender	Lower Criteria	Upper Criteria
Estradiol	pg/mL		<0	>20
Testosterone	nmol/L		<0	>7.34
LH	U/L	Male	<0.3	>2.7
	U/L	Female	<0	>2.0
FSH	U/L	Male	<0	>3.7
	U/L	Female	<0.4	>6.7

Table 2 is used as a guideline to define Estradiol, Testosterone, LH, and FSH abnormal values in this study.

The determination of suppression to prepubertal levels of these hormones is a level less than or equal to the value in the upper criteria of this Table 2. Therefore, the cut-off value of suppression for each parameter is present in Table 3 below.

Table 3 Cut-off for Estradiol, Testosterone, LH and FSH suppression

Parameter	Unit	Gender	Supression
Estradiol	pg/mL		≤ 20
Testosterone	nmol/L		≤ 7.34
LH	U/L	Male	≤2.7
	U/L	Female	<2.0
FSH	U/L	Male	<3.7
	U/L	Female	<6.7

These values above were also used to determine the peak LH and FSH suppression during a GnRH stimulation test. For this study the LH, suppression is defined as peak LH ≤ 2 U/L for female, and peak LH ≤ 2.7 U/L for male. For FSH, suppression is defined as peak FSH ≤ 6.7 U/L for female and 0 ≤ peak FSH ≤ 3.7 U/L for male.

7.8.3 Additional Efficacy Endpoint(s)

Percent of patients with a change from baseline in the following parameters will be summarized in a similar manner as the above categorical secondary efficacy endpoint:

- Increase in predicted adult height during and after treatment with ENANTONE
- Change from baseline for BMI
- Change from baseline in BMD
- Change from baseline in patient height

For these and the other additional efficacy endpoints, descriptive statistics will be provided without inferential comparisons for the end of ENANTONE treatment phase and 3-month intervals and follow-up segments previously described.

- Increase in predicted adult height during and after treatment with ENANTONE
- Change from baseline in standard laboratory tests during and after treatment with ENANTONE
- Incidence rate of polycystic ovarian syndrome during and after treatment with ENANTONE
- Evaluation of long term effect on reproduction
- Change from baseline for BMI

- Change from baseline in BMD
- Change from baseline in patient height

7.9 Pharmacokinetic/Pharmacodynamic Analysis

Not applicable.

7.9.1 Pharmacokinetic Analysis

Not applicable.

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

These are additional outcomes which will be summarized using the FAS analysis set and listed by subject.

They will need to be summarized only using descriptive statistics by 1) ENANTONE treatment phase, 2) Follow-up phase for those who were only treated with ENANTONE 3) Follow-up phase after completion of GnRHa therapy for those who were treated with ENANTONE and then another GnRHa after ENANTONE

- Evaluation of long term effect on reproduction which listed as following
  - Menstruation cycles (females)
  - Pelvic measurement
  - Male sexual characteristic examination
  - Hormonal measurements
  - β-HCG (females)
  - Pregnancy

7.11 Safety Analysis

Safety data will be summarized using the safety analysis set, and individual data will be presented in data listings. Safety outcomes will be analyzed by ENANTONE treatment (high, low dose and overall), and unless specified otherwise will not be stratified by sex. Separate summaries will be performed for the ENANTONE treatment phase and the different segments of the follow-up phase described in section 7.8.

7.11.1 Adverse Events

The primary safety outcome is the incidence per 100 person years of AEs 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, the number of patient person years at risk and incidence per 100 person years (based on the numbers of events). 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.

The following AE subsets will be similarly tabulated. And system organ class and preferred terms will be sorted in decreasing frequency based on the number of subjects with adverse events in total, male, and female group:

a) AEs related to ENANTONE treatment

b) Most frequent AEs, all AEs with incidence of 3% or greater

c) AEs/SAEs resulting in treatment discontinuation

d) AEs by sex

All AEs will be presented in data listings.

7.11.2 Clinical Laboratory Evaluations

If the data permit, changes in standard laboratory tests (hematology, urine analysis, blood biochemistry, serum bone metabolism biomarkers) will be summarized using descriptive statistics. And by-subject listing will be provided.

7.11.3 Vital Signs

All Vital Signs results will be presented in data listings.

7.11.4 12-Lead ECGs

All ECG results will be presented in data listings.

7.11.5 Other Observations Related to Safety

The physical examination findings and vaginal bleeding (females) growth rate, weight, cranial CT/MRI will be presented in data listings.

7.12 Interim Analysis

Not Applicable.

7.13 Changes in the Statistical Analysis Plan

The statistical analysis in the protocol anticipated sufficient subject numbers to permit the comparing of Low and High dose levels of ENANTONE. At the time of finalizing the SAP it was determined that these types of analyses wouldn't be feasible. Therefore, the proposed Cochran-Mantel-Haenszel test will be omitted.

8.0 REFERENCES

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