Statistical Analysis Plan

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

Study Number: Leuprorelin-4002

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

Statistical Analysis Plan

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

SAP Version V3.0

May 28, 2025

Sponsor: Takeda (China) International Trading Co., Ltd.

Project period: December, 2021 to April, 2025

Statistical analysis: LinkDoc Technology (Beijing) Co., Ltd.

Statement

The statistical analysis plan is prepared in accordance with ICH-E9 (Statistical Principles for Clinical Trials), the relevant regulations of the National Medical Products Administration (NMPA), and the standard operating procedure of LinkDoc Technology (Beijing) Co., Ltd. And it is refined based on the principles of statistical analysis in the study protocol. The mock shell (including the examples of statistical analysis tables, figures and listings) will be presented as separate documents.

Approval Page

This document has been reviewed and approved as the statistical analysis plan for this study. This document shall enter into force on the date of the last signature.

Author:

[redacted] LinkDoc Technology (Beijing) Co., Ltd. [redacted]	Signature	Date [DD-MM-YYYY]

Reviewed by:

[redacted] LinkDoc Technology (Beijing) Co., Ltd. [redacted]	Signature	Date [DD-MM-YYYY]
[redacted] LinkDoc Technology (Beijing) Co., Ltd. [redacted]	Signature	Date [DD-MM-YYYY]
[redacted] LinkDoc Technology (Beijing) Co., Ltd. [redacted]	Signature	Date [DD-MM-YYYY]
[redacted] Takeda (China) International Trading Co., Ltd. Statistician	Signature	Date [DD-MM-YYYY]
[redacted] Takeda (China) International Trading Co., Ltd. Medical advisor	Signature	Date [DD-MM-YYYY]
[redacted] Takeda (China) International Trading Co., Ltd. [redacted]	Signature	Date [DD-MM-YYYY]

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List of Abbreviations and Terms

Abbreviations or terminology	Explanation
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification
BA/CA	Bone age/Chronological age
BMI	Body Mass Index
CI	Confidence Interval
CPP	Central Precocious Puberty
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
FMV	First Morning Void
FSH	Follicle Stimulating Hormone
GnRH	Gonadotropin-releasing Hormone
GnRHa	Gonadotropin-releasing Hormone Analogs
hCG	Human Chorionic Gonadotropin
HPGA	Hypothalamic-pituitary-gonadal-axis Function
IRB	Institutional Review Board
IEC	Independent Ethics Committee
ITT	Intention-To-Treat (enrolled analysis population)
LFT	Liver Function Test
LH	Luteinizing Hormone
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
PTE	Pre-treatment Events
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SOC	System Organ Class
SS	Safety Analysis Set (Safety Analysis Population)
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal
WHODRUG	WHODrug Dictionaries

1 Study Objectives

1.1 Primary Objectives

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

1.2 Secondary Objectives

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

2 Study Design

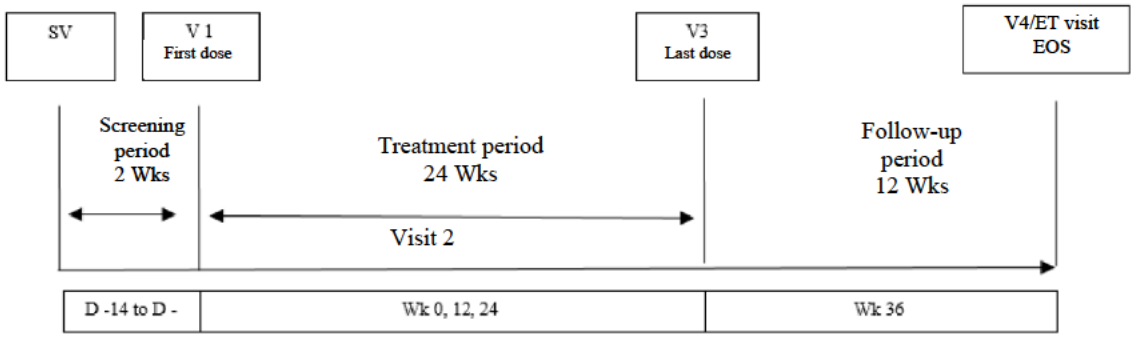
2.1 Overall Design

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

The subjects will receive an injection of leuprorelin acetate depot 11.25mg 3M every 12 weeks. Pharmacokinetic studies in adults demonstrated that the quarterly formulation of 11.25 mg Leuprorelin is steadily released over 12 weeks period [3]. Each dose of the drug will be administered in outpatient hospital setting by appropriate site staff and the date of each administration will be registered on the clinical record of each child. Parents/ legal guardians of patients will be actively contacted some days before the injections to ensure them to follow the administration protocol.

Patients will be received an s.c. injection of study drug at V1, V2, V3. GnRHa stimulation will be repeated at screening visit and V2, V3 (before every s.c. injection of study drug) or at early termination. Basal LH and FSH level testing (gonadotropins and sex steroids) will be repeated at screening visit and V2, V3, V4 (before every s.c. injection of study drug) or at early termination. In this study, height and weight measurement will be performed at screening visit and V1, V2, V3, V4 (before every s.c. injection of study drug) or at early termination. Physical exams and pubertal staging will be performed at screening visit and V1, V2, V3, V4 (before every s.c. injection of study drug) or at early termination. And a BA x-ray will be taken once at the screening visit, as well as V2, V3, and V4 (before every s.c. injection of the study drug), or at early termination; the Gn in the first morning void (FMV) will be tested at the screening visit, as well as V1, V2, V3, and V4 (before each s.c. injection of the study drug), or at early termination. Adverse events will be collected and reported in this study at each study visit or at early termination, and treatment-emergent adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Figure 2-1-1 Schematic of Study Design



V = Visit, D = Day Wk = Week, SV = Screening Visit, EOS = End of Study, ET = Early Termination

2.2 Study Population

The subject population in this study will be the children diagnosed with CPP who develop secondary sexual characteristics before the age of 8 years in girls or before the age of 9 years in boys.

Only those who meet all of the following inclusion criteria and none of the exclusion criteria will be eligible for the enrollment.

2.2.1 Inclusion Criterion

For inclusion in the study, the subjects had to fulfill all of the following criteria:

1. In the opinion of the investigator, the subject and/or parent(s) or legal guardian are capable of understanding and complying with protocol requirements.
2. The subject or the subject's parent(s) or legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.;
3. Early appearance of secondary sexual characteristics: Girls ≤8 years, Boys≤9 years;
4. Body weight ≥20 kg;
5. According to the National Consensus Statement in China (2015), CPP is diagnosed when secondary sexual characteristics appeared before the age of 8 years in girls and 9 years in boys, a peak LH level > 5.0 IU/L with LH/FSH > 0.6 in stimulating test; evidence of gonadal development by ultrasonography (multiple ovarian follicles ≥ 4 mm in any ovary or uterine enlargement in females or testicular volume ≥ 4 mL in males); advanced BA ≥ 1 year; linear growth acceleration with higher GV than normal children. BA is determined by Greulich and Pyle standards or Tanner-Whitehouse 3 (TW3) standards at screening.

6. A male subject who is nonsterilized and sexually active with a female partner of childbearing potential agrees to use adequate contraception from signing of informed consent throughout the duration of the study and for 90 days after last dose.

7. A female subject of childbearing potential who is sexually active with a nonsterilized male partner agrees to use routinely adequate contraception from signing of informed consent throughout the duration of the study and for 90 days after last dose of study medication.

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

2.2.2 Exclusion Criteria

Those who meet any of the following criteria will be excluded from this study:

1. The subject has received any investigational compound within 30 days prior to Screening

2. The subject has received GnRHa treatment in a previous clinical study or as a therapeutic agent;

3. The subject is an immediate family member, study site employee, or is in a dependant relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress;

4. The subject has any findings in his/her medical history, physical examination, or safety clinical laboratory tests giving reasonable suspicion of underlying disease that might interfere with the conduct of the trial;

5. The subject has any concomitant medical condition that, in the opinion of the investigator, may expose a subject to an unacceptable level of safety risk or that affects subject compliance;

6. The subject has any screening abnormal laboratory value that suggests a clinically significant underlying disease or condition that may prevent the subject from entering the study; or the subject has: creatinine ≥1.5 mg/dL, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) 2 times the upper limit of normal (ULN), or total bilirubin 2.0 mg/dL, with AST/ALT elevated above the limits of normal values;

7. The subject has a history or clinical manifestations of significant adrenal or thyroid diseases or intracranial tumor OR has a history of malignant disease;

8. The subject has a history of hypersensitivity or allergies to leuprorelin, or related compounds including any excipients of the compound;

9. The subject has a diagnosis of peripheral precocious puberty;

10. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to the Screening Visit;

11. Subject or parent(s), at the discretion of the investigator, is unlikely to comply with the protocol or is unsuitable for any of other reason;

12. If female, the subject is pregnant, breastfeeding, or planning to become pregnant before, during, or within 1 month after the end of the study; or planning to donate ovums during this period;

13. If male, the subject intends to donate sperm during the course of this study or for 90 days thereafter;

2.3 Sample Size

The calculated sample size of 70, 58, 44 and 29 was based on the assumption that the proportion of LH peak value suppression with GnRH stimulation is 80%, 85%, 90% and 95% respectively and a two-sided 95% confidence interval (CI) with a precision width of 0.2. Since the actual proportion of LH peak value suppression with GnRH stimulation in Chinese remains unknown, a conservative sample size of 70 was determined. Considering the drop-out rate 10% - 15%, a total number of 80 subjects are planned to be enrolled. This study encourages sites to enroll subjects competitively, and each site enrolls at least 15 ~ 25 subjects. Within each site, eligible subjects will be enrolled until the site's subject quota has been reached.

2.4 Study Drug and Administration Method

The study drug for this study is leuprorelin acetate depot 11.25mg 3M. The administration method is as follows: CPP subjects with body weight ≥20 kg will receive the recommended dose of leuprorelin acetate depot 11.25 mg subcutaneous administration (SC) every 12 weeks based on the standard of 30～180μg/kg/4w. It is not recommended to exceed 180 μg/kg.

2.5 Excluded Medications, Procedures, and Treatments

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

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

2.6 Subject Termination or Premature Withdrawal from the Study

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

The criteria for subject termination or withdrawal are as follows:

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

Liver function test (LFT) Abnormalities

Study drug should be discontinued immediately with appropriate clinical follow up (including repeat

laboratory tests, until a subject's laboratory profile has returned to normal/baseline status), if the following circumstances occur at any time during study medication treatment:

- ALT or AST >8 × ULN, or
- ALT or AST 5 × ULN and persists for more than 2 weeks, or
- ALT or AST 3 × ULN in conjunction with elevated total bilirubin 2 × ULN or international normalized ratio (INR) 1.5, or clinical features of jaundice
- ALT or AST 3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (5%).

2. Significant protocol deviation. The discovery after the first dose of study medication that the subject failed to meet protocol inclusion criterion or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.

3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.

4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the CRF.

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

5. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.

6. Pregnancy. The subject is found to be pregnant.

Note: If the subject is found to be pregnant, the subject must be withdrawn immediately.

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

8. Other

3 Endpoint

3.1 Primary Endpoints

- Percentage of subjects achieving LH peak value suppression in the GnRH stimulation test at Week 24.

Definition: The percentage of subjects with LH peak value ≤3.0 IU/L in the GnRH stimulation test at Week 24 relative to the total number of subjects in the corresponding analysis population. The LH peak value is the maximum LH value detected at 0, 30, 60 and 90 minutes after injection of the stimulation drug.

3.2 Secondary Endpoints

- The percentage of subjects with Tanner stage regression or no progression at Week 24 compared with Baseline.

Definition: relative to the last available valid Tanner stage before the first administration of the leuprorelin acetate depot 11.25mg 3M, the percentage of subjects with regression or no progression in Tanner stage at Week 24 relative to the total number of subjects in the corresponding analysis population.

Progression of Tanner stage is defined as meeting any of the following conditions:

1) Tanner stage (left) increased compared with the baseline.

2) Tanner stage (right) increased compared with the baseline.

3) Pubic hair develops when there was none at the baseline.

No progression of Tanner stage is defined as all of the following conditions being met simultaneously:

1) Tanner stage (left) is the same as the baseline

2) Tanner stage (right) is the same as the baseline

3) Presence or absence of pubic hair is the same as the baseline

If Tanner stage does not meet the definition of progression, such status is classified as regression or no progression. Further, if Tanner stage meets the definition of no progression, the status is classified as no progression; if Tanner stage does not meet the definition of progression or no progression, the status is classified as regression.

- Basal LH and FSH level of subjects at Baseline, Week 24, Week 36

Definition: Basal LH and FSH values obtained from LH and FSH tests of subjects at baseline, Week 24, and Week 36.

- The percentage of subjects with decreased ratio of bone age over chronological age at Week 24 compared with Baseline.

Definition: The percentage of subjects with decreased ratio of bone age over chronological age (BA/CA) at Week 24 compared with the Baseline relative to the total number of subjects in the corresponding analysis population.

- Decrease in first morning voided (FMV) urinary Gn at Week 24 compared with Baseline.

1) The percentage of subjects with decreased ratio of urinary LH level in the first morning void (FMV) urinary Gn test at Week 24 compared with the Baseline.

Definition: The percentage of subjects with decreased ratio of urinary LH level in the first morning void (FMV) urinary Gn test at Week 24 among the total number of subjects in the corresponding analysis population, relative to the last available valid urinary LH level before the first administration of the leuprorelin acetate depot 11.25mg 3M.

2) The percentage of subjects with decreased ratio of urinary FSH level in the first morning void (FMV) urinary Gn test at Week 24 compared with the baseline.

Definition: The percentage of subjects with decreased ratio of urinary FSH level in the first morning void (FMV) urinary Gn test at Week 24 among the total number of subjects in the corresponding analysis population, relative to the last available valid urinary FSH level before the first administration of the leuprorelin acetate depot 11.25mg 3M.

- Incidence of treatment-emergent adverse events (TEAEs)

Definition: The percentage of subjects who experience any treatment-emergent adverse event after the first use of the study drug relative to the total number of subjects in the corresponding analysis

population. A TEAE refers to an untoward medical occurrence that occurs in a subject from the first administration of the study drug to 12 weeks after the last administration; such event is not necessarily causally related to the treatment.

3.3 Description of Relevant Definitions

- Baseline definition

For basic demographic characteristics (age, gender, ethnicity), bone age, BA/CA, predicted adult height, GnRH stimulation test (LH peak value, FSH peak value), LH and FSH (basal LH value, basal FSH value), the results from the screening visit will be taken as baseline values;

For height and weight, BMI, growth rate, estradiol/testosterone, gonads ultrasonography, pubertal stage, first morning void (FMV) urinary Gn (urinary LH value, urinary FSH value), the last available valid measurement prior to the first administration of the leuprorelin acetate depot 11.25mg 3M will be used as the baseline values.

4 Analysis Set

The analysis populations for this study include the enrolled analysis population, the safety analysis population, and the termination analysis population.

Enrolled Population:

All eligible subjects enrolled in this study, i.e., all subjects enrolled in this study who meet the inclusion criteria and do not meet any of the exclusion criteria, regardless of whether they receive the study drug, will be included in this analysis set. Unless otherwise specified, the primary and secondary study endpoints (except for adverse event analysis), and baseline characteristics of subjects will be analyzed based on the enrolled population.

For the subjects with significant protocol deviation in this population, the final decision on whether the data affected by the significant protocol deviation is included in the final analysis will be determined at the data review meeting.

Safety Population:

All included patients who have been under treatment with Leuprorelin or who are first prescribed Leuprorelin, receive at least one dose and complete one follow-up visit. A supplementary analysis of the primary study endpoints will be performed based on the safety population as per the actual data of the safety population. The analysis of drug exposure, adverse events and concomitant medications will be based on the safety population.

Completion of one follow-up is defined as subjects with at least one post-baseline data available. Post-baseline data include the results of the following examinations: vital signs, growth rate, weight, height, BMI, concomitant medications, Tanner stage assessment, gonads ultrasonography, bone age, BA/CA, hematology, urinalysis, clinical chemistry, contraceptive consultation (if applicable), electrocardiogram, estradiol or testosterone, FMV urinary Gn, stimulation test, basal LH and FSH, AE assessment, PTE, physical examination, concomitant non-drug therapy, etc.

Discontinuation population:

Patients who discontinue the use of Leuprorelin, are lost to follow-up, withdraw from the study or are dead. Discontinuation analysis will be based on the discontinuation population.

5 Statistical Analysis

5.1 General Principles

Descriptive analyses are the primary focus of this study and no preplanned hypothesis testing will be performed.

All statistical analyses will be programmed and calculated by SAS 9.4 statistical analysis software.

Continuous indicators will be described by number of cases (missing numbers), arithmetic mean, standard deviation, median, 25th and 75th percentile, minimum and maximum; discrete indicators will be described by number of cases and percentages, with a 95% confidence interval if necessary;

Unless otherwise specified, all statistical analysis results will be presented by gender group.

Unless otherwise specified, all missing data will not be imputed.

In this study, MedDRA_28_0_Chinese and WHO_DD_V3.02_2025-06_Chinese coding dictionaries (version numbers will be adjusted based on actual conditions) will be used to code relevant medical events and drugs used.

5.2 Subject Disposition

Describe the distribution of all screened and included patients in the study, including the number of screened subjects, the number and percentage of subjects who failed screening, the reason and percentage of screening failure, the number and percentage of included patients, the number and percentage of subjects with early termination of treatment, the reason and percentage of early termination of treatment, the number and percentage of subjects with study termination, the reason and percentage of study termination, the number and percentage of subjects with protocol deviation, the number and percentage of protocol deviation, the number and percentage of subjects with different types of protocol deviation, and the number of different types of protocol deviation.

Describe the distribution of subjects in each analysis set, including the number of subjects in each analysis set (including the enrolled population, safety population, and discontinuation population); describe the number and percentage of subjects enrolled at each site; list the excluded subjects in the enrolled population and safety population (including subject number, age, gender, reason for exclusion, etc.); list subjects with protocol deviations (including subject number, age, gender, severity, protocol deviation type, and specific description).

5.3 Baseline Characteristics of Subjects

The description of baseline characteristics will be based on the enrolled population.

The basic information of baseline characteristics of subjects will be described according to general

principles, mainly including:

• Baseline demographics: age, gender, ethnicity, height, weight, body mass index (BMI), bone age, BA/CA, predicted adult height, growth rate; Where BMI=weight (kg)/height $(m)^2$, BMI can be described in sections according to WHO classification criteria (based on different ages, BMI grade is divided into severely thinness, thinness, normal, overweight and obesity). The criteria C is summarized as follows, corresponding to age:

- ✧ Severe thinness: BMI<-3SD;
- ✧ Thinness: -3SD≤BMI<-2SD;
- ✧ Normal: -2SD≤BMI≤1SD;
- ✧ Overweight: 1SD<BMI≤2SD;
- ✧ Obesity: 2SD ≤ BMI, see Appendix A [1] for specific classification criteria.

The demographic data of subjects will be presented in listings.

• Prior medical history and concomitant diseases/pre-treatment events: presence or absence of prior medical history, name of medical history, presence or absence of concomitant diseases/pre-treatment events, name of disease/pre-treatment events. The names of disease/pre-treatment event will be presented in the form of SOC (System Organ Class) and PT (Preferred Term). The prior medical history and a list of concomitant diseases/pre-treatment events of the subjects will be presented in listings.

The prior medical history refers to any significant condition or disease related to the disease under study that has recovered at or prior to signing informed consent, and any significant condition or disease related to the disease under study that has healed within 1 year prior to signing informed consent; concomitant disease refers to is a significant condition or disease that is still present at the time of signing the informed consent form, including clinically significant abnormal laboratory values, electrocardiogram, or physical examination abnormalities at screening; a pre-treatment event refers to all untoward medical occurrences that occur in the subjects who have signed the informed consent to participate in the study before the use of any study drug.

• Prior medication history: presence or absence of medication history, names of drugs. Specific drugs will be summarized and analyzed according to ATC therapeutic classification categories (ATC-2) and Preferred Names. A list of prior medication history list for subjects will be presented in listings.

The prior medication is any medication related to eligibility criteria that has been discontinued at or within 1 month prior to signing informed consent.

• Information on estradiol/testosterone tests at baseline: presence or absence of estradiol test, quantitative test results for estradiol, qualitative test results for estradiol, presence or absence of testosterone test, quantitative test results for testosterone, qualitative test results for testosterone.

• Results of gonadal ultrasound examinations at baseline: For females, describe pelvic ultrasound information, including presence or absence of pelvic ultrasound, the volume of the left ovary, the volume of the right ovary, uterine size, follicle volume, number of follicles; for males, describe presence or absence of gonadal ultrasound, the left testicular volume, and the right testicular volume.

• GnRH stimulation LH peak value, GnRH stimulation FSH peak value, LH peak value/FSH

peak value during the subject's baseline period.

• Pubertal staging (i.e., Tanner staging) of subjects at baseline: presence or absence of Tanner staging assessment, Tanner stage (left), Tanner stage (right), and presence or absence of pubic hair.

5.4 Drug Exposure

Drug exposure will be summarized by treatment duration of leuprolide based on the enrolled population. The duration of treatment with leuprolide is defined as the time interval from the first injection of leuprolide to the last injection of leuprolide in the subjects. The overdose of leuprolide will also be summarized.

The use of leuprolide will be described in accordance with general principles, Including: duration of treatment, duration of drug exposure, actual number of leuprorelin injections, whether the first injection of leuprorelin is received, whether the second injection of leuprorelin is received, whether the third injection of leuprorelin is received, actual dose administered for the first injection (μg/kg/4w), intended dose for the first injection (μg/kg/4w), actual dose administered for the second injection (μg/kg/4w), intended dose for the second injection (μg/kg/4w), actual dose administered for the third injection (μg/kg/4w), intended dose for the third injection (μg/kg/4w), average actual dose administered (μg/kg/4w), average intended dose (μg/kg/4w), cumulative actual dose administered (mg), cumulative intended dose (mg), number of times for the actual dose in subjects exceeding 180 μg/kg/4w, number of times for the intended dose in subject exceeding 180 μg/kg/4w, and relative dose intensity. The relevant definitions or calculation formulas are as follows:

1) Duration of treatment (days) = date of last injection of leuprorelin for the subject - date of first injection of leuprorelin for the subject + 1;

2) Duration of drug exposure (days) = date of last injection of leuprorelin for the subject - date of first injection of leuprorelin for the subject + 84;

3) The mean actual dose administered (ug/kg/4w) is equal to the mean of the actual dose administered (ug/kg/4w) of all non-missing injections of leuprolide for the subject;

4) The mean intended dose (ug/kg/4w) is equal to the mean of all non-missing intended doses of leuprolide injections (ug/kg/4w) for the subject;

5) Cumulative actual dose administered (mg) is equal to the sum of all non-missing actual doses of leuprolide injections (mg) for the subject;

6) Cumulative intended dose (mg) is equal to the sum of all non-missing intended doses of leuprorelin injections (mg) for the subject;

7) Relative dose intensity = [Cumulative actual dose administered (mg) / Cumulative intended dose (mg)] × 100%;

8) Intended dose (ug/kg/4w) = Intended dose (ug/kg) / 3 = [Intended dose (mg) × 1000 / Body weight (kg)] / 3;

9) Actual dose administered (ug/kg/4w) = Actual dose administered (ug/kg)/actual time interval (4w) from current injection to the next injection of leuprolide (4w) = [actual dose administered (mg)*1000/body weight (kg)]/[(date of next injection - date of current injection)/28. If there is no next injection, fill in the actual time interval with three 4Ws;

Overdose of leuprolide will be described in accordance with general principles, including presence

or absence of overdose, number of overdose occurrences, presence or absence of related AE, preferred term for related AE, causes for overdose. The relevant definitions or calculation formulas are as follows:

10) Leuprolide overdose is defined as a situation where the subject intentionally or accidentally receives a dose of leuprolide that exceeds the dose assigned to the subject in the study protocol;

11) The number of overdose occurrences is equal to the number of "Yes" recorded for "Whether the study drug is overdosed" in all drug overdose records.

The administration of leuprolide to the subjects is present in listings.

5.5 Concomitant Treatment

The concomitant medications and concomitant non-drug therapies for the subjects will be described in accordance with general principles based on the safety population, Including: presence or absence of concomitant medication, name of medication, reason for medication, presence or absence of concomitant non-drug therapy, reason for non-drug therapy. The same individual subject can have one or more reasons for medication/non-drug treatment, and the number and percentage of cases with different reasons for use will be counted separately. The denominator of percentage calculation will be the number of non-missing subjects in the safety population. The number and percentage of subjects using each specific drug will be summarized by ATC classification system and common terminology of World Health Organization. A list of concomitant medications and a list of concomitant non-drug therapies for subjects will be presented in listings.

Concomitant medication is defined as any drugs administered to the subject other than the study drug from the time of signing the informed consent form to the end of the study. That is, a drug is considered a concomitant medication if it meets either of the following conditions: ① The "whether it is ongoing" status is "Yes", and the start date of medication is earlier than the study completion date or study termination date; ② The "whether it is ongoing" status is "No", the start date of medication is earlier than the study completion date or study termination date, and the end date of medication is later than the date of signing the informed consent form.

Concomitant non-drug therapy is defined as any non-drug therapy received by the subject from the time of signing the informed consent form to the end of the study. That is, a therapy is considered a concomitant non-drug therapy if it meets either of the following conditions: ① The "whether it is ongoing" status is "Yes", and the start date of therapy is earlier than the study completion date or study termination date; ② The "whether it is ongoing" status is "No", the start date of therapy is earlier than the study completion date or study termination date, and the end date of therapy is later than the date of signing the informed consent form.

5.6 Primary Study Endpoint

The analysis of the primary study endpoint will be based on the enrolled population.

Describe the number and percentage of subjects achieving LH peak value suppression in the GnRH stimulation test at Week 12 and Week 24, and estimate their 95% confidence interval using Clopper-pearson method. A subject is considered not to achieve LH peak value suppression if the LH peak value of the GnRH stimulation test at Week 12 and Week 24 is missing.

The trend of the percentage of subjects achieving LH peak value suppression in the GnRH stimulation test at Week 12 and Week 24 will be presented in figures by gender, with 95% confidence intervals

estimated by Clopper-pearson method.

The subjects' GnRH stimulation LH values by visit will be presented in listings.

A sensitivity analysis will be performed for the primary study endpoint, i.e., if a subject has missing LH peak value in the GnRH stimulation test at Week 12 and Week 24, the primary study endpoint will be analyzed after the nearest available measurement from Week 12 and Week 24 (non-baseline) is used as a missing imputation.

5.7 Secondary Study Endpoint

The analysis of the secondary study endpoint will be based on the enrolled population. The following descriptive analyses by gender will be performed separately for the secondary study endpoints according to the general principles:

1) The percentage of subjects with Tanner stage regression or no progression at Week 24 compared with Baseline.

Describe the number and percentage of subjects with Tanner stage regression or no progression at Week 24 compared with Baseline, and estimate the 95% confidence interval using the Clopper-Pearson method. A subject is considered to have no regression or no progression in Tanner stage if the Tanner staging result at Week 24 is missing.

The Tanner staging results by visit will be presented in listings.

A sensitivity analysis will be performed for this endpoint, i.e., if a subject has a missing Tanner staging result at Week 24, this endpoint will be analyzed after the nearest available measurement from Week 24 (non-baseline) is used as a missing imputation.

2) Basal LH and FSH level of subjects at Baseline, Week 24, Week 36

The distribution of LH and FSH test results (including basic LH levels and basic FSH levels) in subjects at Baseline, Week 24, and Week 36 will be described using the number of cases, mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum values. Trend graphs of basal LH and box plots of basal FSH change trends will be plotted separately for subjects by gender at baseline, Week 24, and Week 36.

The baseline LH and FSH values for subjects by visit will be presented in listings.

A sensitivity analysis will be performed for this endpoint, i.e. if the results of basal LH and FSH tests at baseline, Week 24, or Week 36 for a subject are "<xx.xx", "xx.xx" will be used for imputation; if there are still missing values, the 0-minute results of the stimulation test during the same visit period will be used for imputation before the analysis of this indicator.

3) The percentage of subjects with decreased ratio of bone age over chronological age (BA/CA) at Week 24 compared with the Baseline.

Describe the number and percentage of subjects with decreased ratio of bone age over chronological age (BA/CA) at Week 24 compared with Baseline and estimate their 95% confidence interval using Clopper-pearson method. A subject is considered not to achieve decreased ratio of BA/CA if the BA/CA value is missing at Week 24.

The bone age/chronological age (BA/CA) results by visit will be presented in listings.

A sensitivity analysis will be performed for this endpoint, i.e., if a subject has missing BA/CA value at Week 24, this endpoint will be analyzed after the nearest available measurement from Week 24

(non-baseline) is used as a missing imputation.

4) The percentage of subjects with decrease in first morning voided (FMV) urinary Gn at Week 24 compared with Baseline.

Describe the number and percentage of subjects with decreased urinary LH and decreased urinary FSH values in the urinary Gn test results of the first morning void (FMV) at Week 24 compared with Baseline, separately, and estimate their 95% confidence intervals using Clopper-pearson method.

For urinary LH and FSH values in urinary Gn test results of the first morning void (FMV) at Baseline and Week 24, any value that is <0.05 should be recorded as "<0.05". If both the Baseline and Week 24 results are "<0.05", the assessment of such decrease will be treated as missing. If there is at most one "<0.05" result, a comparison can be performed. See Appendix B for the reasons of above processing.

If a subject has a missing value for an indicator in the urinary Gn test results of the first morning void (FMV) at Baseline or Week 24, the subject will be considered not to achieve a decrease in that indicator of the FMV urinary Gn.

The urinary Gn test results of the first morning void (FMV) for the subjects by visit will be presented in listings.

Two sensitivity analyses will be conducted separately for each of the two indicators of this endpoint. For the first sensitivity analysis, if a subject has a missing value for an indicator in urinary Gn test results of the first morning void (FMV) at Week 24, this indicator will be analyzed after the nearest available measurement from Week 24 (non-baseline) is used as a missing imputation. Sensitivity analysis will be performed using the Gn results of the first morning void (FMV) collected by EDC directly for the second time. If the urinary Gn test results of the first morning void (FMV) for the subject at Baseline or week 24 were missing, it was considered that he/she did not achieve a decrease in that indicator of the FMV urinary Gn.

5) Incidence of treatment-emergent adverse events (TEAEs)

The analysis of adverse events will be based on the safety population. The number of cases, number of occurrences, and incidence of TEAEs will be analyzed. All adverse events will be coded using MedDRA_28_0_Chinese (the version number will be adjusted based on the actual situation).

The number of cases, number of occurrences and incidence of all AEs, TEAEs, SAEs, adverse events of special interest (AESIs), AEs leading to discontinuation, AEs leading to dose interruption, AEs leading to dose reduction, AEs related to study drug, AEs leading to trial withdrawal, AEs leading to death, AEs leading to death, and AEs with Grade 3 and above will be summarized separately.

Relevant characteristic information of adverse events will be described, including: severity (i.e., CTCAE grade), outcome, causal relationship with the study drug leuprolide, relationship with study procedures, and frequency of occurrence.

The distribution of all AEs, TEAEs, SAEs, AESIs, AEs leading to discontinuation, AEs leading to dose interruption, AEs leading to dose reduction, AEs with Grade 3 and above, AEs related to the study drug, AEs leading to trial withdrawal, and AEs leading to death will be summarized according to the SOC and PT in the MedDRA coding system.

The lists of adverse events, adverse events related to the study drug and serious adverse events will be presented listings.

The relevant definitions of adverse events are as follows:

An adverse event (AE) is defined as any untoward medical occurrence in a clinical investigation subject first administered a drug

A treatment-emergent adverse event (TEAE) is an untoward medical occurrence that occurs in a subject from the first administration of the study drug to 12 weeks after the last administration of the study drug; it does not necessarily have to have a causal relationship with this treatment.

A serious adverse event (SAE) is any untoward medical occurrence occurring at any dose level that meets one of the following criteria: a. results in death; b. life-threatening; c. requirements for hospitalization or prolongation of hospitalization; d. results in permanent or significant disability/incapacity; e. leads to a congenital anomaly/birth defect.; f. Is an important medical event that satisfies any of the following: 1. May require intervention to prevent items a through e above; 2. May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

Adverse events of special interest (AESIs) are scientific and medical events specifically related to the product or study: a. injection site reactions, b. emotional instability, c. hypersensitivity, d. convulsions, e. slipped capital femoral epiphysis.

Adverse events leading to discontinuation will be defined as specific AEs leading to discontinuation of the study drug Leuprorelin acetate depot 11.25mg 3M.

Adverse events leading to dose interruption will be defined as specific AEs that result in the interruption of the use of study drug Leuprorelin acetate depot 11.25mg 3M.

Adverse events leading to dose reduction will be defined as specific AEs that result in the dose reduction of the study drug Leuprorelin acetate depot 11.25mg 3M.

Adverse events related to the study drug are the specific adverse events that are causally related to the study drug Leuprorelin acetate depot 11.25mg 3M.

5.8 Analysis of other Variables

Other indicators will be analyzed based on the enrolled population. The following descriptive analyses of estradiol and testosterone by gender will be performed according to the general principles:

The distribution of estradiol/testosterone test results (including quantitative results of estradiol tests, qualitative results of estradiol tests, quantitative results of testosterone tests, and qualitative results of testosterone tests) in subjects at Baseline, Week 12, Week 24, and Week 36 will be described using the number of cases, mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum. Additionally, the differences between the quantitative results of estradiol/testosterone tests at Week 12, Week 24, and Week 36 and those at baseline will be described separately; contingency tables will be used to describe the changes in the qualitative results of estradiol/testosterone tests at Week 12, Week 24, and Week 36 compared with Baseline.

The list of estradiol/testosterone results by visit will be presented in listing.

5.9 Discontinuation Analysis

The discontinuation analysis will be based on the discontinuation population. The number and percentage of subjects whose study termination is caused by adverse events, death, or other reasons will be calculated separately, and the tolerability of leuprolide will be evaluated through the termination rate.

5.10 Additional Analysis

The following supplemental analyses will be performed to assess the robustness of the study results.

1) Conduct two supplementary analyses for the primary study endpoint: i. In the enrolled population, the analysis will be based on the non-missing data, i.e. if the LH peak value values of the GnRH stimulation test at Week 12 and Week 24 are missing, the results will be considered as unknown and will not be included in the denominator for calculating the percentage, and then the primary study endpoint will be analyzed. The analysis method is the same as that in Section 5.6; ii. The primary study endpoint will be analyzed based on the safety population, if applicable.

2) Supplemental analyses will be performed on the enrolled population for the following three secondary study endpoints:

- The percentage of subjects with Tanner stage regression or no progression at Week 24 compared with Baseline
- The percentage of subjects with decreased ratio of bone age over chronological age at Week 24 compared with Baseline
- The percentage of subjects with a decrease in Gn of the first morning void (FMV) at Week 24 compared with the baseline (For the Gn results of the first morning void at Baseline and Week 24, re-processed data will be used, see Part 4) in Section 5.7).

The analysis will be conducted based on non-missing data. Specifically, if a subject has missing data for a secondary study endpoint at Week 24, the result will be regarded as unknown and will not be included in the denominator for percentage calculation. The secondary study endpoint will then be analyzed using the same method as described in Section 5.7.

5.11 Handling of Missing Values and Outliers

For time variables involved in the analysis that require imputation: if the year is missing, no imputation will be performed; if the month is missing and median imputation (06/30) does not cause logical issues, median imputation will be adopted, and if there is a logical issue, the handling will be determined based on specific circumstances; if the day is missing and median imputation (15) does not cause logical issues, median imputation will be used; if logical issues arise, the handling will depend on the specific situation.

For the imputation of the occurrence date of an adverse event (AE) (if needed), it will be performed in a way that maximizes the chance of the event being classified as a treatment-emergent adverse

event (TEAE). Specifically: if the year is missing, directly impute the first leuprolide injection date; if the month is missing and the occurrence year matches the year of the first leuprolide injection date, impute the first leuprolide injection date; if the month is missing and the occurrence year differs from the year of first leuprolide injection date, then impute the first day of the occurrence year; if the day is missing and the year and month of occurrence match those of the first leuprolide injection date, impute first leuprolide injection date ; if the day is missing and the year and month of occurrence differ from those of the first leuprolide injection date , then impute as the first day of occurrence month.

Unless otherwise specified, no imputation will be performed for other data.

Whether a value is an outlier will be judged based on the actual condition of the data. Records identified as outliers will be handled accordingly after data management queries and medical review.

5.12 Interim Analysis

The cutoff date for data collection of the interim analysis in this study is planned as August 31, 2023.

For subjects whose primary endpoint or each secondary endpoint can be completely defined by the cutoff date of data collection for the interim analysis, the corresponding endpoints will be analyzed using the methods described in Sections 5.6 and 5.7.

For subjects whose primary endpoint or each secondary endpoint cannot be completely defined by the cutoff date of data collection for the interim analysis, relevant descriptions will be made for the available data on LH peak value in GnRH stimulation test, Tanner stage, basal LH and FSH levels, bone age/chronological age (BA/CA), Gn of first morning void (FMV), and treatment-emergent adverse events.

5.13 Explanation of Inconsistency with the Protocol

The contents of this SAP that are inconsistent with the protocol are summarized as follows:

1. The definition of the enrolled population in Section 13.5 of the protocol refers to all eligible subjects enrolled in this study, and the above definition is refined in this SAP, as shown in Section 4.

2. Section 13.6 of the Protocol stipulates that all analyses will be based on observed data without imputation of missing data. This SAP will perform imputation for some time variables, and the imputation rules are described in Section 5.11.

Appendices

Appendix A BMI Grading Criteria by WHO for Children Aged 5-19 years [1]

Table 6-1-3 BMI Classification Criteria for 5-19 Years Old (Male)

Month	SD3neg	SD2neg	SD1neg	SD0	SD1	SD2
61	12.118	13.031	14.071	15.264	16.645	18.259
62	12.115	13.027	14.066	15.262	16.648	18.273
63	12.114	13.024	14.063	15.26	16.653	18.29
64	12.114	13.022	14.061	15.26	16.659	18.308
65	12.114	13.021	14.06	15.262	16.667	18.328
66	12.115	13.021	14.06	15.264	16.676	18.35
67	12.117	13.021	14.061	15.268	16.686	18.374
68	12.121	13.023	14.063	15.274	16.699	18.399
69	12.125	13.026	14.067	15.28	16.712	18.427
70	12.129	13.03	14.071	15.288	16.727	18.456
71	12.135	13.035	14.077	15.296	16.743	18.487
72	12.141	13.04	14.083	15.306	16.761	18.52
73	12.148	13.047	14.09	15.317	16.78	18.554
74	12.155	13.053	14.098	15.328	16.799	18.589
75	12.163	13.061	14.107	15.341	16.82	18.626
76	12.171	13.069	14.116	15.354	16.842	18.665
77	12.18	13.077	14.126	15.368	16.864	18.704
78	12.189	13.086	14.136	15.382	16.888	18.745
79	12.198	13.095	14.147	15.398	16.913	18.788
80	12.208	13.105	14.158	15.414	16.938	18.831
81	12.218	13.115	14.17	15.43	16.964	18.876
82	12.228	13.126	14.183	15.447	16.991	18.922
83	12.239	13.136	14.195	15.465	17.019	18.969
84	12.25	13.148	14.209	15.483	17.047	19.017
85	12.261	13.159	14.222	15.502	17.076	19.066
86	12.272	13.171	14.236	15.521	17.106	19.116
87	12.283	13.183	14.25	15.541	17.136	19.168
88	12.295	13.195	14.265	15.561	17.167	19.22
89	12.307	13.208	14.28	15.581	17.199	19.274
90	12.319	13.221	14.295	15.602	17.231	19.328
91	12.331	13.234	14.311	15.624	17.264	19.383
92	12.343	13.247	14.327	15.646	17.297	19.44
93	12.356	13.26	14.343	15.668	17.331	19.497
94	12.368	13.274	14.36	15.69	17.366	19.555

Month	SD3neg	SD2neg	SD1neg	SD0	SD1	SD2
95	12.381	13.288	14.377	15.713	17.401	19.615
96	12.394	13.302	14.394	15.737	17.437	19.675
97	12.407	13.317	14.412	15.761	17.473	19.736
98	12.42	13.331	14.429	15.785	17.51	19.798
99	12.434	13.346	14.447	15.809	17.548	19.862
100	12.447	13.361	14.466	15.834	17.586	19.926
101	12.461	13.376	14.484	15.86	17.624	19.99
102	12.475	13.392	14.503	15.886	17.663	20.056
103	12.489	13.408	14.523	15.912	17.702	20.123
104	12.503	13.424	14.542	15.938	17.742	20.19
105	12.518	13.44	14.562	15.965	17.783	20.258
106	12.532	13.456	14.582	15.992	17.824	20.327
107	12.547	13.473	14.603	16.02	17.866	20.397
108	12.562	13.491	14.624	16.049	17.908	20.468
109	12.578	13.508	14.646	16.078	17.952	20.54
110	12.594	13.526	14.668	16.108	17.996	20.613
111	12.61	13.545	14.691	16.138	18.04	20.687
112	12.626	13.564	14.714	16.169	18.086	20.763
113	12.643	13.583	14.738	16.201	18.132	20.839
114	12.661	13.603	14.763	16.233	18.179	20.916
115	12.679	13.624	14.788	16.266	18.227	20.994
116	12.697	13.645	14.814	16.3	18.276	21.074
117	12.716	13.667	14.84	16.335	18.326	21.154
118	12.735	13.689	14.867	16.37	18.376	21.234
119	12.755	13.712	14.895	16.406	18.428	21.317
120	12.775	13.735	14.923	16.443	18.48	21.4
121	12.796	13.759	14.952	16.481	18.532	21.483
122	12.817	13.784	14.982	16.519	18.586	21.568
123	12.838	13.808	15.012	16.558	18.64	21.653
124	12.86	13.834	15.043	16.597	18.696	21.739
125	12.882	13.86	15.074	16.638	18.751	21.826
126	12.905	13.886	15.106	16.679	18.808	21.914
127	12.928	13.913	15.139	16.72	18.865	22.002
128	12.952	13.941	15.172	16.763	18.923	22.09
129	12.976	13.969	15.206	16.806	18.982	22.18
130	13.001	13.998	15.241	16.85	19.042	22.271
131	13.026	14.027	15.276	16.894	19.102	22.362
132	13.051	14.056	15.312	16.939	19.163	22.452
133	13.077	14.087	15.348	16.985	19.224	22.544
134	13.103	14.117	15.385	17.031	19.287	22.637

Month	SD3neg	SD2neg	SD1neg	SD0	SD1	SD2
135	13.13	14.148	15.422	17.078	19.349	22.729
136	13.157	14.18	15.461	17.126	19.413	22.822
137	13.185	14.212	15.499	17.175	19.477	22.915
138	13.213	14.245	15.539	17.224	19.542	23.009
139	13.241	14.278	15.578	17.273	19.607	23.104
140	13.27	14.312	15.619	17.324	19.674	23.199
141	13.3	14.347	15.66	17.375	19.741	23.293
142	13.33	14.382	15.702	17.427	19.808	23.389
143	13.36	14.417	15.745	17.48	19.877	23.485
144	13.391	14.453	15.788	17.533	19.946	23.581
145	13.422	14.49	15.833	17.588	20.015	23.677
146	13.454	14.528	15.877	17.643	20.086	23.774
147	13.487	14.566	15.923	17.698	20.157	23.871
148	13.52	14.605	15.969	17.755	20.229	23.969
149	13.554	14.644	16.016	17.812	20.302	24.067
150	13.588	14.684	16.063	17.87	20.375	24.165
151	13.622	14.724	16.112	17.929	20.449	24.263
152	13.658	14.766	16.161	17.989	20.524	24.362
153	13.693	14.807	16.21	18.049	20.599	24.46
154	13.729	14.849	16.26	18.11	20.675	24.559
155	13.766	14.892	16.311	18.171	20.751	24.658
156	13.802	14.935	16.362	18.233	20.829	24.757
157	13.839	14.979	16.414	18.296	20.906	24.856
158	13.877	15.023	16.466	18.359	20.984	24.954
159	13.915	15.067	16.519	18.422	21.062	25.053
160	13.953	15.112	16.572	18.486	21.14	25.152
161	13.991	15.157	16.625	18.55	21.219	25.249
162	14.029	15.202	16.679	18.615	21.298	25.347
163	14.068	15.247	16.733	18.68	21.376	25.444
164	14.107	15.293	16.787	18.744	21.455	25.54
165	14.145	15.338	16.841	18.81	21.534	25.635
166	14.184	15.384	16.895	18.875	21.613	25.731
167	14.222	15.429	16.95	18.94	21.691	25.825
168	14.261	15.475	17.004	19.005	21.77	25.918
169	14.299	15.521	17.058	19.07	21.848	26.011
170	14.337	15.566	17.113	19.135	21.926	26.103
171	14.375	15.611	17.167	19.2	22.004	26.194
172	14.414	15.657	17.221	19.265	22.081	26.284
173	14.451	15.702	17.275	19.329	22.158	26.373
174	14.489	15.747	17.329	19.394	22.235	26.462

Month	SD3neg	SD2neg	SD1neg	SD0	SD1	SD2
175	14.526	15.791	17.382	19.458	22.311	26.549
176	14.563	15.836	17.435	19.522	22.387	26.635
177	14.6	15.88	17.489	19.585	22.462	26.72
178	14.636	15.924	17.541	19.649	22.537	26.804
179	14.672	15.968	17.594	19.712	22.611	26.887
180	14.708	16.011	17.647	19.774	22.685	26.969
181	14.744	16.054	17.699	19.837	22.758	27.051
182	14.779	16.097	17.75	19.899	22.831	27.13
183	14.814	16.14	17.802	19.96	22.903	27.21
184	14.848	16.182	17.853	20.022	22.975	27.288
185	14.882	16.224	17.904	20.082	23.046	27.365
186	14.916	16.265	17.954	20.143	23.116	27.441
187	14.95	16.306	18.004	20.203	23.186	27.515
188	14.982	16.347	18.053	20.262	23.255	27.59
189	15.015	16.387	18.103	20.321	23.324	27.662
190	15.047	16.427	18.151	20.38	23.391	27.734
191	15.078	16.466	18.199	20.438	23.459	27.805
192	15.109	16.505	18.247	20.495	23.525	27.875
193	15.14	16.543	18.295	20.552	23.591	27.943
194	15.17	16.581	18.342	20.608	23.656	28.011
195	15.199	16.619	18.388	20.664	23.721	28.078
196	15.228	16.656	18.434	20.72	23.785	28.143
197	15.257	16.692	18.479	20.774	23.847	28.207
198	15.285	16.728	18.524	20.829	23.91	28.271
199	15.312	16.763	18.568	20.882	23.972	28.334
200	15.339	16.798	18.612	20.936	24.032	28.395
201	15.365	16.833	18.655	20.988	24.093	28.456
202	15.391	16.867	18.698	21.04	24.152	28.515
203	15.417	16.9	18.741	21.091	24.211	28.573
204	15.441	16.933	18.782	21.142	24.269	28.63
205	15.465	16.965	18.823	21.192	24.327	28.687
206	15.489	16.997	18.864	21.242	24.383	28.742
207	15.512	17.028	18.904	21.291	24.439	28.797
208	15.534	17.059	18.944	21.34	24.494	28.85
209	15.556	17.089	18.983	21.388	24.549	28.903
210	15.577	17.118	19.022	21.435	24.603	28.954
211	15.598	17.147	19.06	21.482	24.656	29.005
212	15.618	17.176	19.097	21.528	24.708	29.054
213	15.637	17.204	19.134	21.574	24.76	29.103
214	15.656	17.231	19.171	21.619	24.811	29.15

Month	SD3neg	SD2neg	SD1neg	SD0	SD1	SD2
215	15.674	17.258	19.207	21.664	24.861	29.197
216	15.692	17.284	19.242	21.708	24.911	29.243
217	15.709	17.31	19.277	21.751	24.959	29.287
218	15.725	17.335	19.311	21.794	25.008	29.331
219	15.741	17.36	19.344	21.836	25.055	29.373
220	15.756	17.383	19.377	21.877	25.102	29.415
221	15.771	17.407	19.41	21.918	25.147	29.455
222	15.784	17.429	19.442	21.958	25.193	29.496
223	15.798	17.452	19.473	21.998	25.237	29.534
224	15.811	17.473	19.504	22.037	25.281	29.572
225	15.823	17.495	19.535	22.076	25.324	29.609
226	15.834	17.515	19.564	22.114	25.366	29.646
227	15.845	17.535	19.594	22.151	25.408	29.681
228	15.855	17.554	19.622	22.188	25.449	29.716

Table 6-1-4 BMI Classification Criteria for 5-19 Years Old (Female)

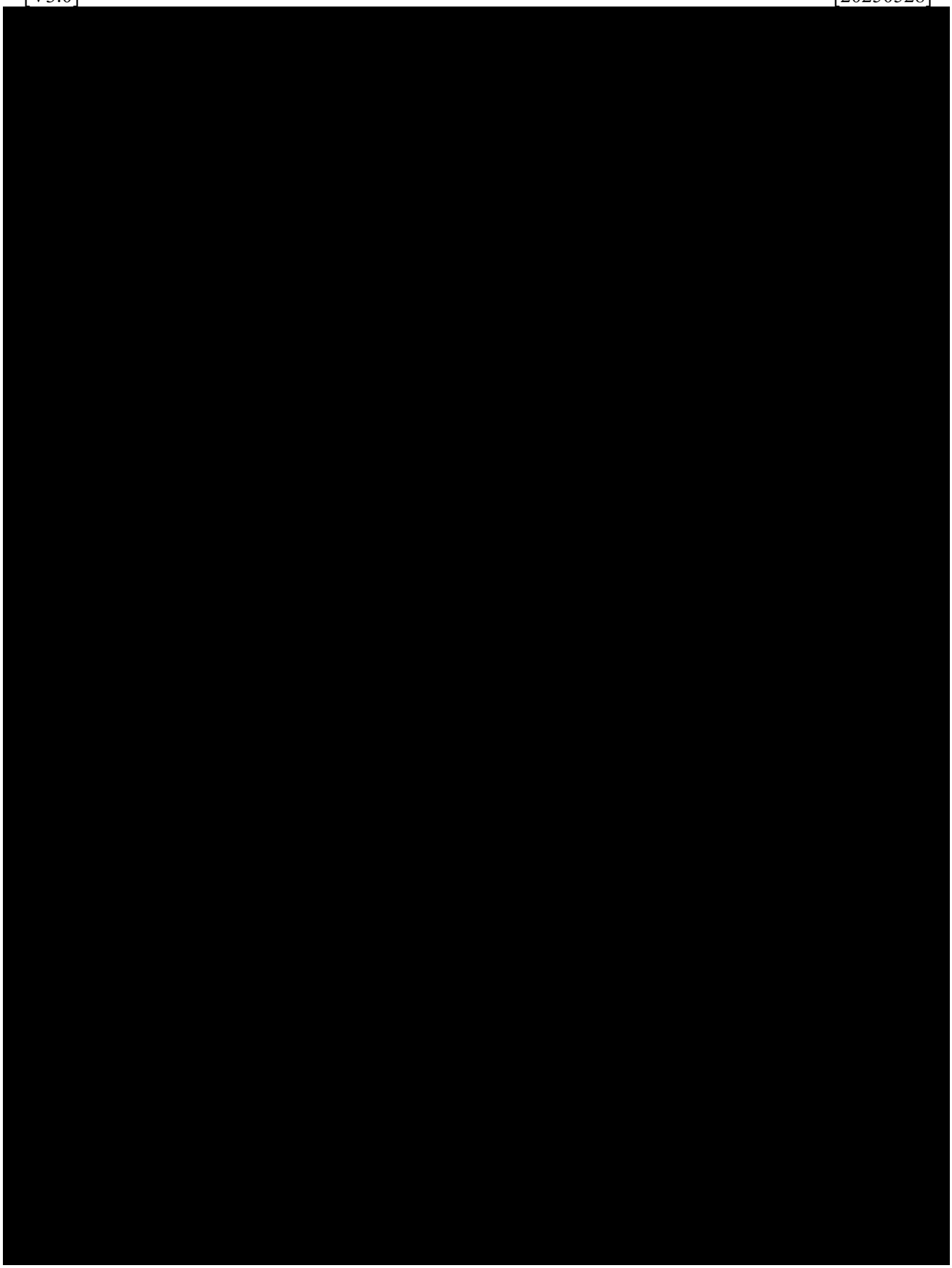
Month	SD3neg	SD2neg	SD1neg	SD0	SD1	SD2
61	11.77	12.748	13.891	15.244	16.87	18.858
62	11.763	12.741	13.885	15.243	16.879	18.886
63	11.757	12.734	13.881	15.243	16.889	18.915
64	11.752	12.728	13.876	15.244	16.9	18.946
65	11.746	12.723	13.872	15.245	16.911	18.977
66	11.742	12.718	13.869	15.246	16.923	19.009
67	11.737	12.714	13.866	15.249	16.936	19.042
68	11.733	12.71	13.864	15.252	16.95	19.077
69	11.73	12.706	13.863	15.255	16.964	19.112
70	11.727	12.703	13.862	15.259	16.979	19.148
71	11.725	12.701	13.862	15.264	16.995	19.185
72	11.723	12.7	13.862	15.27	17.011	19.224
73	11.722	12.699	13.863	15.276	17.029	19.264
74	11.721	12.698	13.865	15.283	17.047	19.305
75	11.721	12.699	13.867	15.291	17.067	19.347
76	11.722	12.7	13.87	15.3	17.087	19.391
77	11.723	12.701	13.874	15.31	17.108	19.436
78	11.725	12.704	13.879	15.32	17.131	19.482
79	11.727	12.707	13.885	15.331	17.154	19.529
80	11.731	12.711	13.892	15.344	17.179	19.578
81	11.735	12.716	13.899	15.357	17.204	19.628
82	11.74	12.721	13.907	15.372	17.231	19.68
83	11.745	12.728	13.916	15.387	17.259	19.734
84	11.751	12.735	13.927	15.404	17.289	19.789
85	11.758	12.743	13.938	15.421	17.319	19.845
86	11.766	12.752	13.95	15.44	17.35	19.903
87	11.774	12.762	13.963	15.459	17.383	19.963
88	11.783	12.772	13.976	15.48	17.417	20.023
89	11.793	12.783	13.991	15.501	17.452	20.085
90	11.803	12.795	14.007	15.524	17.488	20.149
91	11.814	12.808	14.023	15.548	17.526	20.214
92	11.826	12.822	14.041	15.572	17.564	20.281
93	11.838	12.836	14.059	15.598	17.604	20.349
94	11.851	12.852	14.078	15.625	17.645	20.418
95	11.865	12.868	14.099	15.652	17.687	20.489
96	11.879	12.884	14.12	15.681	17.73	20.561
97	11.895	12.902	14.142	15.711	17.774	20.634
98	11.91	12.92	14.164	15.742	17.82	20.709
99	11.927	12.94	14.188	15.773	17.866	20.784

Month	SD3neg	SD2neg	SD1neg	SD0	SD1	SD2
100	11.944	12.959	14.212	15.806	17.914	20.862
101	11.962	12.98	14.238	15.839	17.962	20.94
102	11.98	13.001	14.264	15.874	18.012	21.019
103	11.998	13.023	14.291	15.909	18.062	21.1
104	12.018	13.045	14.318	15.945	18.113	21.181
105	12.037	13.068	14.346	15.982	18.166	21.263
106	12.057	13.092	14.375	16.019	18.219	21.346
107	12.078	13.115	14.404	16.058	18.272	21.429
108	12.099	13.14	14.434	16.096	18.326	21.513
109	12.12	13.165	14.465	16.136	18.381	21.599
110	12.141	13.19	14.496	16.176	18.437	21.684
111	12.163	13.216	14.527	16.217	18.493	21.77
112	12.185	13.242	14.559	16.258	18.551	21.857
113	12.208	13.269	14.592	16.3	18.608	21.944
114	12.231	13.296	14.625	16.343	18.666	22.031
115	12.254	13.323	14.659	16.386	18.725	22.12
116	12.278	13.352	14.694	16.43	18.785	22.208
117	12.302	13.38	14.729	16.475	18.846	22.298
118	12.327	13.41	14.764	16.52	18.907	22.388
119	12.352	13.439	14.801	16.566	18.969	22.479
120	12.378	13.47	14.838	16.613	19.032	22.57
121	12.404	13.501	14.876	16.661	19.096	22.663
122	12.43	13.533	14.914	16.71	19.161	22.755
123	12.458	13.565	14.954	16.76	19.226	22.849
124	12.485	13.598	14.994	16.81	19.293	22.943
125	12.514	13.631	15.035	16.861	19.36	23.038
126	12.542	13.666	15.076	16.914	19.429	23.134
127	12.572	13.7	15.119	16.967	19.498	23.231
128	12.602	13.736	15.162	17.021	19.568	23.328
129	12.632	13.772	15.206	17.076	19.639	23.426
130	12.663	13.81	15.251	17.132	19.712	23.525
131	12.695	13.847	15.297	17.188	19.785	23.624
132	12.727	13.885	15.343	17.246	19.859	23.725
133	12.76	13.925	15.39	17.304	19.933	23.825
134	12.793	13.964	15.438	17.364	20.009	23.927
135	12.827	14.004	15.487	17.424	20.086	24.029
136	12.861	14.045	15.536	17.485	20.163	24.131
137	12.896	14.087	15.586	17.546	20.241	24.234
138	12.931	14.129	15.637	17.609	20.32	24.338
139	12.967	14.171	15.688	17.672	20.4	24.442

Month	SD3neg	SD2neg	SD1neg	SD0	SD1	SD2
140	13.003	14.214	15.74	17.736	20.48	24.546
141	13.04	14.258	15.793	17.8	20.561	24.651
142	13.077	14.302	15.846	17.865	20.642	24.756
143	13.114	14.346	15.899	17.931	20.724	24.861
144	13.151	14.391	15.953	17.997	20.806	24.967
145	13.189	14.436	16.008	18.063	20.889	25.072
146	13.227	14.481	16.062	18.13	20.972	25.177
147	13.265	14.526	16.117	18.197	21.055	25.282
148	13.303	14.572	16.172	18.264	21.138	25.387
149	13.341	14.618	16.227	18.331	21.222	25.491
150	13.379	14.663	16.282	18.399	21.305	25.596
151	13.418	14.709	16.338	18.466	21.388	25.699
152	13.456	14.755	16.393	18.533	21.471	25.802
153	13.494	14.8	16.448	18.601	21.554	25.905
154	13.531	14.846	16.503	18.668	21.637	26.007
155	13.569	14.891	16.558	18.735	21.719	26.107
156	13.606	14.936	16.612	18.801	21.8	26.207
157	13.643	14.981	16.667	18.868	21.882	26.307
158	13.68	15.025	16.721	18.934	21.962	26.405
159	13.717	15.07	16.775	18.999	22.042	26.501
160	13.753	15.113	16.828	19.064	22.122	26.598
161	13.788	15.157	16.881	19.129	22.201	26.693
162	13.824	15.2	16.934	19.193	22.279	26.786
163	13.859	15.243	16.986	19.257	22.357	26.879
164	13.893	15.285	17.037	19.32	22.433	26.97
165	13.927	15.327	17.088	19.382	22.509	27.06
166	13.961	15.368	17.139	19.444	22.584	27.149
167	13.994	15.408	17.188	19.504	22.658	27.235
168	14.026	15.448	17.238	19.565	22.731	27.321
169	14.058	15.488	17.286	19.624	22.803	27.406
170	14.089	15.526	17.334	19.682	22.874	27.489
171	14.119	15.564	17.38	19.74	22.943	27.57
172	14.149	15.601	17.427	19.797	23.012	27.65
173	14.179	15.638	17.472	19.852	23.079	27.727
174	14.207	15.674	17.516	19.907	23.145	27.804
175	14.235	15.709	17.56	19.961	23.21	27.879
176	14.262	15.743	17.603	20.013	23.273	27.951
177	14.288	15.776	17.644	20.065	23.336	28.023
178	14.314	15.809	17.685	20.115	23.396	28.091
179	14.338	15.841	17.725	20.164	23.456	28.159

Month	SD3neg	SD2neg	SD1neg	SD0	SD1	SD2
180	14.362	15.871	17.764	20.212	23.514	28.224
181	14.385	15.901	17.802	20.26	23.57	28.289
182	14.408	15.93	17.839	20.305	23.625	28.35
183	14.429	15.958	17.874	20.35	23.679	28.411
184	14.45	15.985	17.909	20.393	23.731	28.469
185	14.469	16.012	17.943	20.436	23.782	28.525
186	14.488	16.037	17.976	20.477	23.832	28.58
187	14.507	16.062	18.008	20.517	23.88	28.634
188	14.524	16.085	18.039	20.556	23.927	28.684
189	14.541	16.108	18.069	20.594	23.972	28.734
190	14.557	16.13	18.098	20.631	24.017	28.782
191	14.572	16.151	18.126	20.666	24.06	28.828
192	14.586	16.172	18.153	20.701	24.101	28.873
193	14.6	16.191	18.179	20.734	24.141	28.915
194	14.613	16.21	18.205	20.767	24.18	28.956
195	14.625	16.228	18.229	20.798	24.218	28.996
196	14.636	16.245	18.253	20.829	24.254	29.034
197	14.647	16.261	18.275	20.858	24.29	29.07
198	14.656	16.277	18.297	20.886	24.324	29.105
199	14.666	16.291	18.318	20.914	24.356	29.138
200	14.674	16.305	18.338	20.94	24.388	29.17
201	14.682	16.318	18.357	20.966	24.418	29.201
202	14.689	16.331	18.376	20.99	24.448	29.23
203	14.695	16.343	18.393	21.014	24.476	29.257
204	14.701	16.354	18.411	21.037	24.503	29.283
205	14.707	16.365	18.427	21.059	24.53	29.308
206	14.711	16.375	18.443	21.08	24.555	29.333
207	14.716	16.384	18.458	21.101	24.58	29.355
208	14.719	16.393	18.472	21.121	24.603	29.376
209	14.722	16.401	18.486	21.14	24.626	29.398
210	14.725	16.409	18.499	21.159	24.649	29.418
211	14.728	16.417	18.512	21.177	24.67	29.436
212	14.73	16.424	18.525	21.194	24.691	29.455
213	14.731	16.431	18.537	21.212	24.712	29.472
214	14.733	16.437	18.548	21.228	24.731	29.489
215	14.734	16.443	18.56	21.244	24.75	29.505
216	14.734	16.448	18.571	21.26	24.769	29.52
217	14.735	16.454	18.581	21.276	24.788	29.536
218	14.735	16.459	18.592	21.291	24.805	29.55
219	14.735	16.463	18.601	21.306	24.823	29.564

Month	SD3neg	SD2neg	SD1neg	SD0	SD1	SD2
220	14.734	16.468	18.611	21.32	24.84	29.577
221	14.734	16.473	18.621	21.334	24.856	29.589
222	14.733	16.477	18.63	21.348	24.873	29.602
223	14.732	16.48	18.639	21.362	24.889	29.614
224	14.731	16.484	18.648	21.375	24.905	29.626
225	14.729	16.488	18.657	21.388	24.92	29.637
226	14.728	16.491	18.665	21.401	24.935	29.649
227	14.726	16.494	18.673	21.414	24.951	29.659
228	14.724	16.497	18.681	21.427	24.965	29.67



Appendix B Description of LH and FSH Test Results for Urinary Gn of the First morning void (FMV)

Description of Test Results

Study title: [redacted] lticenter, Single-arm and Prospective Study to Assess the Efficacy and Safety of [redacted] e Treatment of CPP

Client: Lin [redacted] Beijing) Co., Ltd.

Partner: Ji [redacted] -Test Med-Tech Co., Ltd.

According [redacted] of both parties, Jiangsu Macro&Micro-Test Med-Tech Co., Ltd., entrusted by LinkDoc Technology (Beijing) Co., Ltd., conduct tests on luteinizing hormone (LH) and follicle stimulating hormone (FSH) in urine samples in accordance with the criteria of *Collection and Processing of Human Urine Samples* (GB/T38735-2020) in the above study of leuprolide acetate, and issue test reports accordingly. The names of the corresponding detection kits are: Detection Kit for Luteinizing Hormone (LH) (Fluorescent Immunochromatographic Assay), Detection Kit for Follicle Stimulating Hormone (FSH) (Fluorescent Immunochromatographic Assay). See Table 1 for the limit of detection, linear interval and limit of blank range of the kits.

Table 1. Limit of Detection, Linear Interval and Limit of Blank Range of the Lits

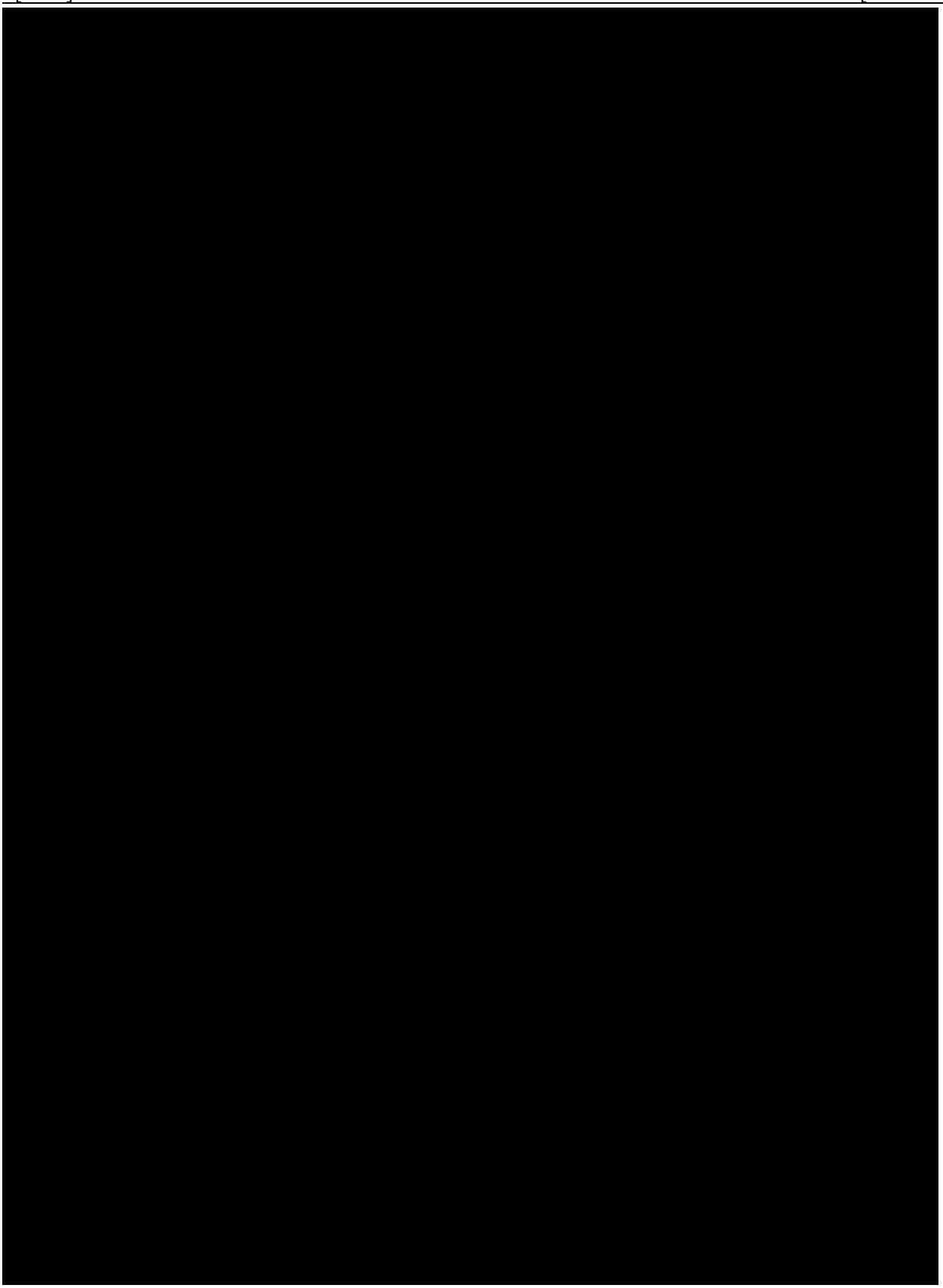
Product name	Limit of detection	Linear interval	Limit of blank	Urine
Detection Kit for Luteinizing Hormone (LH) (Fluorescent Immunochromatographic Assay)	0.05mIU/mL	0.05-100mIU/mL	0.02mIU/mL	Urine
Detection Kit for Follicle Stimulating Hormone (FSH) (Fluorescent Immunochromatographic Assay)	0.05mIU/mL	0.05~100mIU/mL	0.02mIU/mL	Urine
Detection Kit for Luteinizing Hormone (LH) (Fluorescent Immunochromatographic Assay)	0.5mIU/mL	1~100mIU/mL	1mIU/mL	Blood
Detection Kit for Follicle Stimulating Hormone (FSH) (Fluorescent Immunochromatographic Assay)	0.2mIU/mL	1-100mIU/mL	1mIU/mL	Blood

We recently received feedback from client that the range values of "FSH < 0.2 mIU/mL" and "LH < 0.5 mIU/mL" appeared in the two test reports of 2025.03.10 and 2025.03.14 tests (see Annex 1 Original Report), which are inconsistent with the previous fixed-value test results. For this reason, we have made the following explanations after conducting an internal investigation.

1. Reasons for the range value in the test results.

Our Detection Kit for Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH) are used to detect LH and FSH in blood and urine. In previous collaborations with other clients, for test results of blood sample, range values are reported for those below the limit of blank, while fixed values are reported for test results of urine sample.

When we provided the urine sample test for LinkDoc Technology (Beijing) Co., Ltd., the Company also reported fixed values for test results of urine sample in accordance with relevant regulations. However, range results such as <0.2 mIU/mL or <0.5 mIU/mL appeared in the test reports dated March 10, 2025, and March 14, 2025, which was inconsistent with the lowest detection limit of 0.05 mIU/mL shown in the technical document. Because the operator judged the reported result as set as the lower limit of quantification of the test for the blood, the result was reported as the range value. (See Table 2)



Incorrect settings	Correct settings
Modified conclusion in concentration reference range ×	Modified conclusion in concentration reference range ×
Name of result determination interval 1 <0.5mIU/mL	Name of result determination interval 1
Modified conclusion in concentration reference range ×	
Name of result determination interval 1 <0.2mIU/mL	

2. Explanation of the effect of incorrect settings of the judgment interval for the test results reported by the instrument on the test results

The reporting format is realized through the setting of the result judgment interval of the instrument, which will not affect the sample testing process, calculation results, nor the authenticity of the data. As shown in Figure 1 below, the same sample is tested by two report forms and the report is output. If the result judgment interval is set, the range value will be output. If the range interval is not set, the fixed value will be reported.

However, the data issued by our company for 0.05 mIU/mL below the limit of detection are based on the data obtained by reporting the fixed value of urine sample. Although there are specific values for the data, the total error of quantitative detection is greater than 30%, which is of low quantitative significance.

Figure 1 Report Results of the Same Sample by Two Reporting Forms

Test Report
Batch No.: [redacted]
Sample ID: [redacted]
Name:
Test item: LH
Concentration: < 0.5 mIU/mL
Tested by:
Test time: April 9, 2025 09:07:51
Statement: This result is for this sample only

Test Report
Batch No.: [redacted]
Sample ID: [redacted]
Name:
Test item: FSH
Concentration: < 0.2mIU/mL
Tested by:
Test time: April 9, 2025 09:07:10
Statement: This result is for this sample only

Test Report
Batch No.: [redacted]
Sample ID: [redacted]
Name:
Test item: LH
Concentration: 0.07mIU/mL
Tested by:
Test time: April 9, 2025 09:08:18
Statement: This result is for this sample only

Test Report
Batch No.: [redacted]
Sample ID: [redacted]
Name:
Test item: FSH
Concentration: 0.05mIU/mL
Tested by:
Test time: April 9, 2025 09:07:32
Statement: This result is for this sample only

3. Explanation of Handling for Reports with Range Values.

Based on the explanations in points 1 and 2, for the samples tested on March 10, 2025, and March 14, 2025, we re-output the original results in accordance with the reporting format for urine samples to obtain new result reports (see Appendix 2: Revised Reports). A comparison of the results involving range values in the two reports is shown in Table 3. Both the reports before and after revision, together with this explanation, will be archived in accordance with relevant requirements and delivered to the client for archiving.

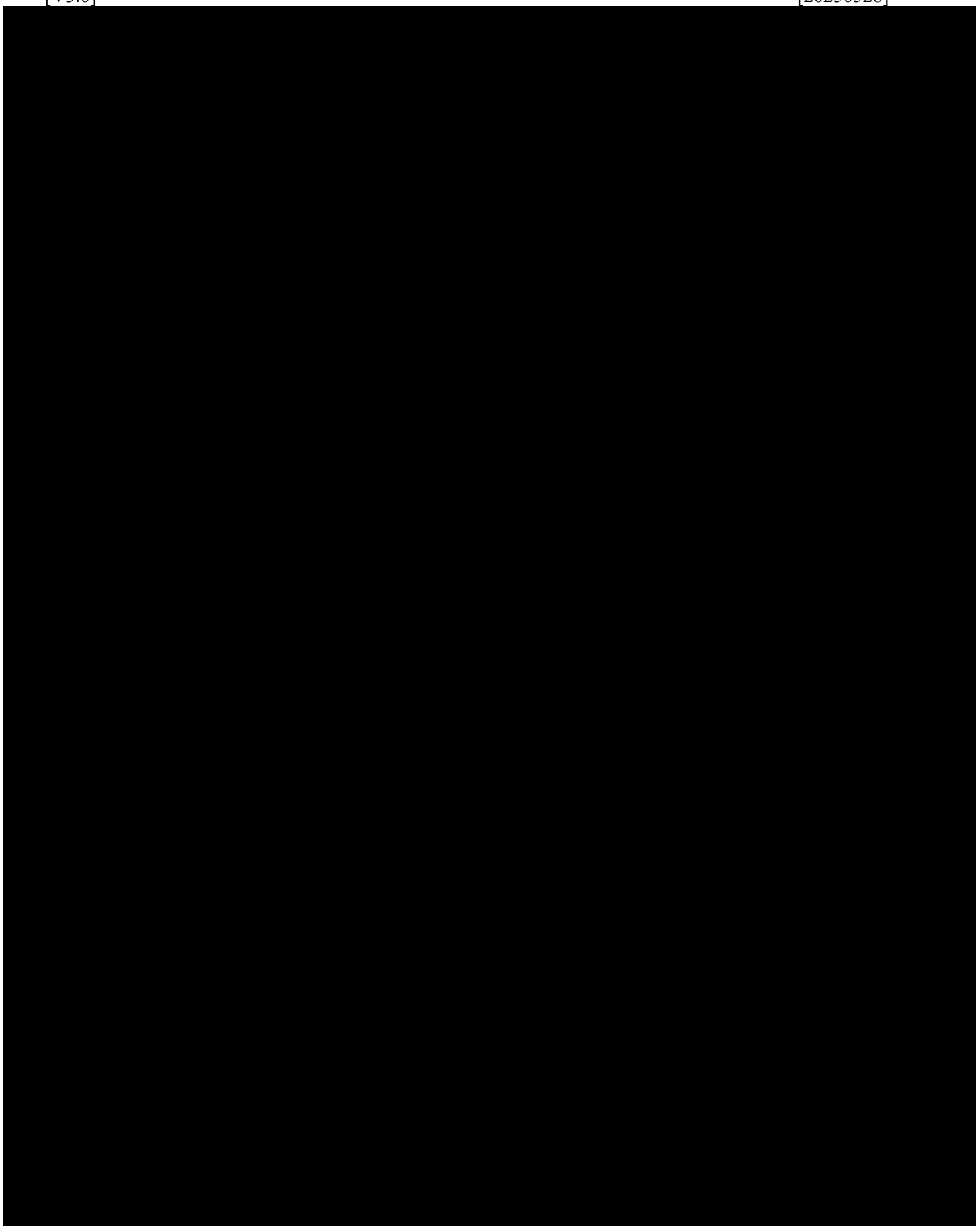


Table 3. Original Test Results and Corrected Results of Samples

Sample receiving hospital	The First Affiliated Hospital, Sun Yat-sen University					Test Results			
						Incorrectly reported results		Corrected results	
Patient No.	Visit number	Gender	Abbreviations of Pinyin	Lot No. of Reagent	Test date	FSH	LH	FSH	LH
[redacted]	V4	Female	YWHA	LH [redacted]	[redacted] 2025	<0.2mIU/mL	<0.5mIU/mL	0.07mIU/mL	0.05mIU/mL
	V4	Female	HURU	FSH [redacted]		0.95mIU/mL	<0.5mIU/mL	0.95mIU/mL	0.04mIU/mL
	V3	Female	PYJL	LH [redacted]	[redacted] 2025	<0.2mIU/mL	<0.5mIU/mL	0.02mIU/mL	0.03mIU/mL
	V3	Female	WCXI	FSH: [redacted]		<0.2mIU/mL	4.93mIU/mL	0.03mIU/mL	4.93mIU/mL

This is hereby explained. Method for issuing subsequent reports: In view of the fact that we have completed the testing of all samples (and there is no need for further testing), currently only find two batches of sample reports (dated [redacted], 2025, and [redacted] 2025) were not inconsistent with the results in previous reports due to personnel operation errors. Therefore, the report is only revised according to the method in Section 3. For the original data in previous reports where the detected concentration is lower than the lower limit of quantification, no revision will be made.

Describe herein.

Jiangsu Macro&Micro-Test M [redacted]

Jiangsu Macro&Micro-Test Med-Tech Co., Ltd.

Document History

Version No.	Version Date	Author	Major Modifications/Comments
V1.0	September 21, 2023	[redacted]	First version, finalized based on Protocol V3.0.
V2.0	December 6, 2023	[redacted]	1.Considering the exposure cycle, an analysis of drug exposure duration is added to the drug exposure status in Section 5.4, with the supplementary calculation formula 2): "Duration of drug exposure (days) = date of last injection of leuprolide for the subject - date of first injection of leuprolide for the subject + 84". The original serial numbers 2) to 10) of the subsequent calculation formulas are postponed to 3) to 11); the section of drug exposure duration in "Table 6.4.1 Description of Leuprolide Use by Subjects – Enrolled Population" of the corresponding statistical analysis table template is added. 2. Due to the mismatch between the calculation formula and the unit, the original formula 8) in the drug exposure of Section 5.4 is revised as follows: Actual dose used (ug/kg/4w) = Actual dose used (ug/kg)/actual time interval (Month) from current injection to the next injection of leuprolide (Month) = [actual dose used (mg)*1000/body weight (kg)]/[(date of next injection - date of current injection)/30.4375. If there is no next injection, fill in the actual time interval with three months; Revised to: 9) Actual dose used (ug/kg/4w) = Actual dose used (ug/kg)/actual time interval (4w) from current injection to the next injection of leuprolide (4w) = [actual dose used (mg)*1000/body weight (kg)]/[(date of next injection - date of current injection)/28. If there is no next injection, fill in the actual time interval with three 4Ws; 3. Add a new Section 5.8 for Analysis of Other Indicators to describe the test results of estradiol/testosterone at each visit and the changes before and after the treatment. Add Section 6.8 of the template of corresponding statistical analysis table, and the numbers of the subsequent sections should be postponed to 6.9, 6.10, and 6.11.

Version No.	Version Date	Author	Major Modifications/Comments
V3.0	May 28, 2025	[redacted]	1. Considering the effect of major protocol deviations on data, add handling measures for data affected by major protocol deviations in Section 4 Enrolled Population. Remove "Drug Exposure" from the analysis of the enrolled population and add it to the analysis based on the safety population. 2. Add the drug exposure duration in "Table 6.4.1 Description of Leuprolide Use by Subjects – Enrolled Population" of the statistical analysis table template corresponding to Section 5.4 Drug Exposure. 3. Revise Section 4) of 5.7: LH and FSH results of urinary Gn of in the first morning void (FMV) require programmatic processing before analysis. Additionally, conduct a sensitivity analysis on data directly collected by EDC system, and modify/add corresponding statistical charts accordingly. 4. Add Section 6.8 of the template of statistical analysis table corresponding to Section 5.8 Analysis of Other Indicators. Subsequent section numbers should be adjusted to 6.9, 6.10 and 6.11. 5. Given the refinement of the enrolled population definition and the imputation of missing values for some time variables in this SAP, add Section 5.13 to explain inconsistencies between the SAP and the Study Protocol. 6. Revise the BMI grading criteria in Section 5.3 and update the information in Appendix B. 7. According to the Protocol, the primary endpoint should display trend changes by visits and genders. Therefore, in sections related to LH suppression in the GnRH stimulation test (e.g., Sections 5.6 and 5.10), add an analysis of LH suppression achieved at Week 12 of the visit in the GnRH stimulation test. 8. Add the list of results corresponding to Sections 5.6, 5.7 and 5.8. 9. Delete original Appendix A, and calculate the predicted adult height using the BP method. After evaluation by the project team and Investigators, this method is found to overestimate adult height and is deemed unsuitable for this study. The project team recommend using the formula developed "based on BP method principles combined with the survey data of nine-province/municipality child physical development in China in year of 2005" (See References 2, 3) to calculate the predicted adult height. Investigators at each site may independently confirm the calculation method for predicted adult height based on professional judgment. The data of predicted adult height exported from the EDC system will be directly used for statistical results.

Note: Compared with the Chinese version, the dictionary version in the English SAP has been updated according to the latest actual situation.

References

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