STATISTICAL ANALYSIS PLAN

A PHASE III, OPEN-LABEL, MULTICENTRE, SINGLE ARM STUDY TO ASSESS THE EFFICACY AND SAFETY OF THE TRIPTORELIN 6-MONTH FORMULATION IN CHINESE PAEDIATRIC PARTICIPANTS WITH CENTRAL PRECOCIOUS PUBERTY

D-CN-52014-244

This statistical analysis plan is based on:
PROTOCOL VERSION AND DATE: 2.0 – 29 APRIL 2022

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Final Version 1.0	09JULY2021
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APPROVAL PAGE

STUDY NUMBER:	D-CN-52014-244
PROTOCOL TITLE:	A phase III, open-label, multicentre, single arm study to assess the efficacy and safety of the triptorelin 6-month formulation in Chinese paediatric participants with central precocious puberty
SAP VERSION:	Final Version 2.0
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The undersigned agree that all required reviews of this document are complete, and approve this Statistical Analysis Plan:

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HISTORY OF CHANGES

Version Number	Date	Description/Rational for change
1.0	09 July 2021	Not Applicable
2.0	19 Apr 2023	• Protocol updated from version 1 to version 2; • Remove PCSA part; • Add details to handle derived data for bone age, growth velocity, oestradiol and testosterone in section 7; • Add details to handle "laboratory values below LLOQ or above ULOQ" in section 5.1. • Remove the description related to estimand

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	Wording Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
BA	Bone Age
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
C	Concomitant
CA	Chronological Age
CI	Confidence Interval
CRF	Case Report Form
CPP	Central Precocious Puberty
eCRF	Electronic Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EOS	End of Study
EMA	European Medicines Agency
FDA	Food and Drug Administration
FSH	Follicle-stimulating Hormone
GnRH	Gonadotropin-releasing Hormone
ICE	Intercurrent Event
ICH	International Conference on Harmonisation
IGF-1	Insulin-like Growth Factor 1
i.m.	Intramuscular
IMP	Investigational Medicinal Product
ITT	Intention-To-Treat
IU	International Units
i.v.	Intravenous

ABBREVIATION	Wording Definition
LH	Luteinising Hormone
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-To-Treat
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NRI	Non-responder imputation
P	Prior
PASS	Power Analysis and Sample Size
PC	Prior and Concomitant
PK	Pharmacokinetic
PN	Preferred Name
PP	Per Protocol
PR	Prolonged Release
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System®
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SI	International System of Units
SOC	System Organic Class
SP	Service Provider
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures and Listings
ULOQ	Upper Limit of Quantification

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to outline the planned analyses to be completed to support the completion of the Clinical Study Report (CSR) for protocol D-CN-52014-244. It describes the rules and conventions to be used in the analysis and presentation of data, the data to be summarised and analysed, including specificities of the statistical analyses to be performed.

Exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP performed will be clearly identified in the respective CSR.

The SAP is to be finalised before first participant in. A separate shell will be provided for tables, figures and listings.

Any deviations from the SAP after database lock will be documented in the CSR (section 9.8 "Changes in the conduct of the study or planned analyses" as per International Conference on Harmonisation (ICH) E3).

2 PROTOCOL OVERVIEW

2.1 Study Objectives and Hypotheses

2.1.1 Primary Objective

The primary objective of the study is to assess the efficacy of the triptorelin 6-month prolonged release (PR) formulation in suppressing luteinizing hormone (LH) levels to prepubertal levels (defined as a peak LH ≤5 IU/L) after intravenous (i.v.) gonadotropin-releasing hormone (GnRH) stimulation at Month 6 (Day 169) in Chinese children with central precocious puberty (CPP).

2.1.2 Secondary Objectives

The secondary objectives of the study are as follows:

- To assess the efficacy in suppressed LH response to GnRH test at Months 3 and 12
- To assess change of basal serum LH and FSH levels at Months 3, 6, 9 and 12
- To assess change of peak serum LH and FSH levels after the GnRH stimulation test at Months 3, 6 and 12
- To assess sex hormone serum concentrations (oestradiol for girls and testosterone for boys) at Months 3, 6, 9 and 12
- To assess height (Z-score [height for age] and percentile for height for age) growth velocity and BA (Greulich and Pyle method) at Months 6 and 12
- To assess sexual maturation at Months 6 and 12
- To assess uterine length in girls and testis volumes in boys at Months 6 and 12
- To assess the change of body weight and BMI at Months 6 and 12
- To assess the safety profile
- To evaluate local tolerability at the injection site immediately and 2 hours after triptorelin injection
- To assess the PK of plasma triptorelin

2.1.3 Hypotheses

The null hypothesis H0: P≤80% versus the alternative hypothesis H1: P>80%, where P is the proportion of children with LH suppression defined as stimulated peak LH ≤5 IU/L after

GnRH stimulation at Month 6.

2.2 Overall Study Design and Investigational Plan

This is an open-label, multicentre, single arm interventional study to evaluate the efficacy and safety of triptorelin 6-month formulation in Chinese paediatric participants with CPP over a period of 12 months.

This study aims to demonstrate that triptorelin 6-month formulation is efficacious in suppressing luteinizing hormone (LH) to prepuberal levels in children with CPP (defined as a peak LH ≤5 IU/L after intravenous (i.v.) gonadotropin-releasing hormone (GnRH) stimulation) at Month 6.

This study will enrol Chinese participants with CPP in girls less than 9 years old and boys less than 10 years old at initiation of triptorelin treatment.

Approximately a total 66 participants (including at least three boys) will be enrolled to be administered intramuscular (i.m.) injections of triptorelin on Day 1 and Month 6 of the study. The triptorelin injection dose will not be adapted based on body weight.

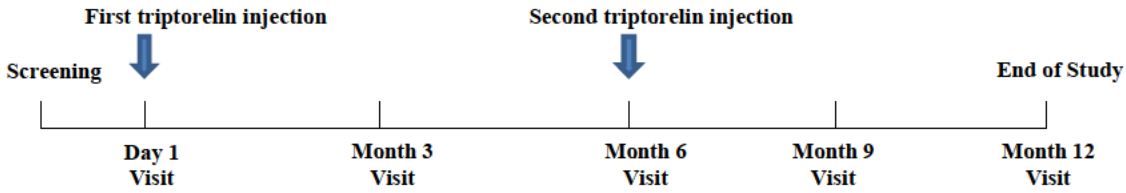
The study consists of a Screening period (the Screening visit will take place up to 28 days before enrolment), during which participants with CPP will be screened for eligibility. Participants will receive triptorelin injections on Day 1 and Month 6 of the study. Participants will have study visits at Screening, Day 1 and at Months 3, 6, 9 and 12 (Figure 1).

Each participant is expected to be enrolled in this study for a minimum of 12 months and up to 13 months (including Screening period).

Participants who complete the study will perform final procedures and assessments at the final visit (Month 12). Participants who withdraw from the study before the completion of the evaluation period will be invited to attend an Early Withdrawal visit to perform early discontinuation procedures and assessments.

The study design is illustrated in Figure 1.

Figure 1 Study Design



2.3 Sample Size Determination and Power

The sample size of this study is estimated based on following assumptions according to global pivotal study DEBIO 8206-CPP-301 [Klein 2016].

- Expected outcome for the proportion of children with a suppressed LH response to the GnRH stimulation test (stimulated peak serum LH ≤5IU/L) at Month 6 is 93%;
- Null proportion is 80%;
- An exact binomial test of a proportion with a one-sided nominal significance level of 0.025 and power =85%;
- Expected common dropout rate =5%.

Under these assumptions, approximately 66 participants (Power Analysis and Sample Size

(PASS) software)) are planned to be enrolled into the study to ensure there are 62 treated participants to confirm the efficacy of the triptorelin 6-month formulation by the proportion of children with a suppressed LH response to the GnRH stimulation test at Month 6.

2.4 Randomisation and Blinding (if applicable)

This is a non-randomised, open-label study. The study treatment assignment will be known to the participants, investigators, study centres, Sponsor, and any Service Provider (SP) affiliated with the study. Access to the data in the Electronic Data Capture (EDC) system is controlled and limited only to authorised personnel for specified data review.

2.5 Schedule of Assessments

Schedule of assessments is presented in Section 8 from the protocol.

2.6 Change from Statistical Section of the Protocol

There is no change in SAP from statistical section of the protocol.

3 PLANNED ANALYSES

3.1 Data Monitoring

No independent Data Monitoring Committee (DMC) will be used in this study.

3.2 Interim Analysis / Primary Analysis

No interim analysis will be performed. If an unplanned interim analysis is deemed necessary, the appropriate sponsor medical director, or designee, will be consulted to determine whether it is necessary to amend the protocol.
No primary analysis will be performed for the primary endpoint at month 6.

3.3 Final Analysis

Final analysis will be done when all participants complete study (Month 12) and after database lock.

4 ANALYSIS SETS

The following populations will be used during statistical analyses:

- **Screened** population: All participants screened (i.e. who signed the ICF).
- **Safety** population: All participants who receive at least one dose of study intervention and have at least one post-baseline safety assessment.
- **Intention-To-Treat** population (ITT): All participants who receive at least one dose of study intervention.
- **Modified Intention-To-Treat population (mITT**): All treated participants having a Month 6 post-baseline assessment of the primary efficacy endpoint.
- **Per protocol** set (PPS): All participants in the mITT after exclusion of the participants who had major protocol deviations that could potentially affect the primary efficacy endpoint outcome for the participants.
- **PK** set (PKS): All participants who receive at least one dose of study intervention and have at least one valid triptorelin concentration.

5 STATISTICAL METHODS/ANALYSES

The statistical analyses will be performed in accordance with ICH E9 guideline and guidelines presented in Section 8.

TigerMed will perform the statistical analysis of this study under the supervision of the Biometry department of IPSEN.

5.1 General Considerations

The precision of the measurement for each continuous variable will be used to determine the number of decimal places to present in tables, figures, and derived listings. Unless otherwise specified, min and max values will be reported with the same decimal as the units of measure; the mean, median and standard deviation (SD), will be reported to 1 greater decimal place, all of them will not be greater than 4 decimal places. Any values that require transformation to standard units (metric or International System [SI]) will be converted with the appropriate corresponding precision.

Percentages of categorical variables will be presented to 1 decimal place unless otherwise specified.

For laboratory values data below the lower limit of quantification (LLOQ) like "<xxx" or "<=xxx", or above the upper limit of quantification (ULOQ) like ">xxx" or ">=xxx", LLOQ or ULOQ (xxx) will be used for calculation of descriptive statistics. The original laboratory values ("<xxx", "<=xxx", ">xxx" or ">=xxx") are presented in the listings.

All statistical analyses will be performed using the SAS® software version 9.4 or above version.

5.1.1 Outputs Presentation

5.1.1.1 Tables Header

Since this is a single-arm study, all summary tables will be presented by Female, Male and Overall.

5.1.1.2 Presentation of Gender Group

Tables, Figures and Listings (TFLs) will be displayed using the following gender group labels, in the order presented: Female, Male, Overall.

5.1.1.3 Presentation of Visits / Timepoints

Summaries by visit will be presented using visit number as collected in the Electronic Case Report Form (eCRF).

Visits in the TFLs will be presented as follows and in the following order:

Long Visit Name	Short Name
Screening (Visit 1)	Scr
Baseline	Bsl
Month 3 (Visit 3)	M3
Month 6 (Visit 4)	M6
Month 9 (Visit 5)	M9
Month 12 (Visit 6)	M12

5.1.2 Descriptive Statistics

All raw and derived variables will be listed and described using summary statistics. For categorical variables, summary statistics will be displayed using descriptive statistics by frequency count and percentages by category. The missing category will be presented if there is at least one missing category for at least one gender group. Except otherwise specified, participants with missing data will be included in the calculation of percentages. For quantitative variables, summary statistics will be displayed using descriptive statistics by number of observations, mean, SD, median, minimum and maximum. Missing data will be displayed.

5.1.3 Baseline Value

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to first IMP administration (including unscheduled assessments). If the assessment time and/or IMP administration time is not collected, the assessment performed on the same day as the first IMP administration will be considered as baseline.

5.1.4 Reference Start Date and Study Day

Reference start date is defined as the day of the first IMP administration.

The day of the first IMP administration will be Day 1. Study day will be calculated as:

- The difference between the event date and the reference date plus one day, if the event is on or after the reference date.

- The difference between the event date and the reference date, if the date of event is prior to the reference date.

Study day will appear in any listings where an assessment date or event date appears.

In case of partial or missing event date, study day will appear missing while any associated durations will be presented based on the imputations described in appendix A2.

5.2 Disposition and Analysis Sets

Following disposition summaries and listings will be provided:

- Summary table with the number and percentages of treated participants per gender and site on the ITT population,
- Summary table with the number and percentage of participants screened, screen failed, reason for screen failures, treated, completed, withdrawn and reason for withdrawal, on the screened population,
- Summary table on duration of participant participation in the study. The definition of the duration of participant participation is from date of consent to the last study visit on the ITT population,
- Listing of dates of visit including duration of participant participation for the treated participants on the ITT population,
- Listing of screen failure participants on the screened population,
- Listing of withdrawal participants on the ITT population.

Following population summaries and listings will be provided on the ITT population:

- Listing of participants violated inclusion criteria,
- Listing of participants fulfilled exclusion criteria,
- Summary of the number and percentage of participants in each analysis population by gender group, based on all treated participants with reasons for exclusion from each analysis population,
- Listing including flag for each analysis population and reason for exclusion from each population.

5.3 Protocol Deviations

An exhaustive list of major protocol deviations that may occur during the course of the study and any action to be taken regarding exclusion of participants from the PPS population is defined in Protocol Deviation Assessment Plan. Major protocol deviations will be determined before database lock of the study, finalised during the data review meeting and documented in a separate document.

Following protocol deviation summary and listing will be provided on the ITT population:

- Number and percentage of participants with major protocol deviations by deviation category (see DV section of Standard Study Data Tabulation Model (SDTM) user guide).
- Number and percentage of participants with major protocol deviations related to COVID-19 by deviation category.
- Listing of major protocol deviations.
- Listing of all protocol deviations by deviation class (e.g. minor/major).
- Listing of all COVID-19 pandemic related protocol deviations by deviation class (e.g. minor/major).

5.4 Demography and Other Baseline Characteristics

All demographic and baseline characteristics summaries and listings will be provided for the ITT, mITT, PPS and safety population. No statistical comparison between gender groups will be performed.

Following summaries will be provided on:

- Demographic variables (age, ethnicity, race),
- Other baseline characteristics (height, weight, BMI, pubertal stage, growth velocity, bone age, chronological age, the difference between bone age and chronological age, ratio of BA:CA),
- Disease characteristics (Age of diagnosis, Time from initial diagnosis of CPP, GnRH-stimulated LH peak, GnRH-stimulated FSH peak, Basal LH, Basal FSH, oestradiol levels and uterine length for girls, testosterone levels and testicular volume for boys).

Listings will also be provided for all the summaries listed above.

5.5 Medical History, Non-drug Therapies, Medications and Surgical Procedures

Medical and surgical history, non-drug therapies and surgical procedures will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) in effect within IPSEN at the time of database lock. Medications will be coded using the latest version of World Health Organization-Drug dictionary in effect within IPSEN at the time of database lock.

Medication, non-drug therapies and surgical procedures start and stop dates will be compared to the date of the first IMP administration to allow classification as either Prior only, Prior and Concomitant, or Concomitant only:

Prior (P)	Start and stop dates prior to the date of the first IMP administration.
Prior and Concomitant (PC)	Start date before the date of the first IMP administration and stop date on or after the date of the first IMP administration.
Concomitant (C)	Start date on or after the date of first IMP administration.

Summary tables on prior medications/non-drug therapies/surgical procedures will include “P” only, summary tables on concomitant medications/non-drug therapies/surgical procedures will include “C” and “PC”.

See detailed rules in appendix A2 for classification of prior and concomitant medication/non-drug therapies, surgical procedures in case of partial/missing date.

The therapeutic class will correspond to the second level of Anatomical Therapeutic Chemical (ATC) code, that is, corresponding to the first 3 figures.

Following summaries, presenting count and percentages of participants will be provided on the ITT population :

- Medical and surgical history by primary system organ class (SOC) and preferred term (PT),
- Prior medications (P) for the study indication by ATC class (ATC level 2) and preferred term PT,
- Concomitant medications (PC, C) for the study indication by ATC class (ATC level 2) and preferred term PT,
- Prior non-drug therapies (P) by primary SOC and PT,
- Concomitant non-drug therapies (PC, C) by primary SOC and PT,
- Prior surgical procedures (P) by primary SOC and PT,
- Concomitant surgical procedures (PC, C) by primary SOC and PT,

Listings will be provided for all the summaries listed above. These listings should include a flag indicating the category (P, PC, C) as described in the table above.

A prohibited medication listing be provided including the following drug: Oestradiol, Testosterone, GnRH analogues (other than triptorelin 6-month formulation),

medroxyprogesterone acetate, growth hormone or Insulin-like Growth Factor 1 (IGF-1), systemic or inhaled steroids (mild topical steroids are permitted) or anticoagulants or drugs which raise prolactin levels.

5.6 Compliance

Compliance with study treatment will be presented as the number and proportion of patients who received the two IMP injections. A listing of treatment compliance will be provided.

5.7 Efficacy

5.7.1 General Considerations

The primary efficacy analysis will be performed on the ITT population. Supportive analysis of the primary efficacy endpoint will be based on the mITT and the PPS population.

The secondary efficacy analyses will be based on the ITT population.

A listing of all efficacy data (raw and derived) should be provided (see listing detail conventions in Appendix A4). Descriptive statistics will be provided for all endpoints.

5.7.1.1 Significance Testing and Estimations

For the primary efficacy endpoint, the summary statistics of number and percentage of participants and the exact two-sided 95% confidence interval (CI) for a binomial proportion will be computed by SAS® using the exact binomial distributions on the ITT (primary population of analysis) population.

For secondary efficacy endpoints related to a change at Months 3, 6, 9 and 12 compared to baseline, the descriptive summary statistics (n, mean, SD, median, minimum, maximum) will be calculated on the ITT. Exact two-sided 95% CIs will also be constructed for all secondary endpoints expressed as percentages.

5.7.1.2 Handling of Dropouts and Missing Data

Diligent attempts will be made to limit the amount of missing data and to follow-up all treated participants to collect the primary and secondary efficacy endpoints for the statistical analysis.

A Non-responder imputation (NRI) method will be used for all definition of response, for instance, participants who discontinue before evaluation of the endpoint (Month 3, Month 6, Month 9 and Month 12) will be declared non-responder.

5.7.1.3 Statistical/Analytical Issues

Adjustments for Covariates

No covariate adjustment analysis is planned in this study.

Interim Analyses and Data Monitoring

No interim analysis will be performed.

Multicentre Studies

No by-centre displays or adjustments for centre are planned for this study.

Multiple Comparisons/Multiplicity

No multiple testing will be performed in this study since this is a single arm study.

5.7.2 Analysis of Primary Efficacy Endpoint

5.7.2.1 Endpoint

LH suppression: defined as a peak LH ≤5 IU/L after intravenous (i.v.) gonadotropin-releasing hormone (GnRH) stimulation in Chinese children with central precocious puberty (CPP).
The primary endpoint is proportion of children with LH suppression at Month 6.

5.7.2.2 Primary Analysis

For the primary efficacy endpoint, the summary statistics of number and percentage of participants and the exact two-sided 95% CI for a binomial proportion will be computed by SAS® using the exact binomial distributions on the ITT.

The SAS code to be used could be presented in Appendix A1.

A listing will be provided including all participants with missing values for the primary endpoint. For these participants, the listing will provide all observed data related to the primary endpoint i.e. all measurements recorded prior to the missing value, any measurements recorded after the missing value, important baseline characteristics, the reason and timing for study discontinuation. The listing will also provide the imputed value(s) (if applicable) used in the primary analysis and any sensitivity analyses.

5.7.2.3 Sensitivity Analysis

Sensitivity analysis of the primary efficacy endpoint will be conducted with the same statistical method based on the mITT and the PPS population.

5.7.2.4 Supplementary Analysis

No supplementary analyses will be performed.

5.7.2.5 Subgroup Analysis

No subgroup analyses will be performed.

5.7.3 Analysis of Secondary Efficacy Endpoints

5.7.3.1 Endpoint

Secondary efficacy endpoints and evaluations are summarised in following table:

Table 1 Secondary Efficacy Endpoints and Evaluations

Measure	Timepoint	Variable	Endpoint
Peak LH after GnRH stimulation test	Month 3 and Month 12 Month 6 and Month 12	LH suppression (stimulated peak LH <=5 IU/L after GnRH stimulation)	• Proportion of children with LH suppression defined as stimulated peak LH <=5 IU/L after GnRH stimulation at Month 3 and 12 • Proportion of children maintaining LH suppression defined as stimulated peak LH <=5 IU/L after GnRH stimulation from Month 6 to 12
Basal LH and FSH	Baseline, Month 3, Month 6, Month 9 and Month 12	LH and FSH concentration	Change in basal serum LH and FSH levels at Months 3, 6, 9 and 12 compared to baseline
Peak LH and FSH after GnRH stimulation test	Baseline, Month 3, Month 6 and Month 12	LH and FSH concentration	Change in peak serum LH and FSH levels at Months 3, 6 and 12 compared to baseline
Pre-pubertal levels of sex steroids	Month 3, Month 6, Month 9 and Month 12 Baseline, Month 3, Month 6, Month 9 and Month 12	oestradiol <=20 pg/mL [<73 pmol/L] in girls or testosterone<=30 ng/dL [<0.8 nmol/L] in boys	• Proportion of children with pre-pubertal levels of sex steroids (defined as oestradiol <=20 pg/mL in girls or testosterone <=30 ng/dL in boys) at Months 3, 6, 9 and 12 • Change in sex steroids levels at Months 3, 6, 9 and 12 compared to baseline
Height (Z-score and percentile for height for age) and growth velocity	Baseline, Month 6, and Month 12	Height (Z-score and percentile for height for age) and growth velocity	• Change in height (Z-score [height for age] and percentile for height for age) and growth velocity at Months 6 and 12 • Height absolute Z-scores and percentiles at Baseline, Months 6, and 12 • Change in Height at Months 6, and 12 compared to baseline

BA (Greulich and Pyle method):CA ratio	Month 6 and Month 12	BA and CA	Proportion of children in whom the BA (Greulich and Pyle method):CA ratio did not rise at Months 6 and 12 relative to baseline (X-ray)
BA and CA and ratio BA:CA	Baseline, Month 6 and Month 12	BA and CA	Change in difference between BA and CA and ratio BA:CA and BA at Months 6 and 12 compared to baseline
Stabilisation of sexual maturation	Month 6 and Month 12	Children who achieve stabilisation of sexual maturation	Proportion of children who achieve stabilisation of sexual maturation at Month 6 and 12 compared to baseline stage using Tanner method
Girls uterine length	Month 6 and Month 12 Baseline, Month 6 and Month 12	Uterine length	• Proportion of girls with regression of uterine length (transabdominal ultrasound) at Months 6 and 12 • Change in uterine length at Months 6 and 12 compared to baseline
Boys testis volumes	Month 6 and Month 12 Baseline, Month 6 and Month 12	Testis volumes	• Proportion of boys with absence of progression of testis volumes (clinical assessment with orchidometer) at Months 6 and 12 • Change in testis volumes at Months 6 and 12 compared to baseline
Body weight and BMI	Month 6 and 12	Body weight and BMI	Change in body weight and BMI at Months 6 and 12 compared to baseline

The SAS code and algorithm of Z-score and percentile for height for age are presented in Appendix (A5).

5.7.3.2 Secondary Analysis

For secondary efficacy endpoints related to a change at Months 3, 6, 9 and 12 compared to baseline, the descriptive summary statistics (n, mean, SD, median, minimum, maximum) will be calculated on the ITT. Exact two-sided 95% CIs will also be constructed for all secondary endpoints expressed as percentages.

GV cm/y, Height, Weight, BMI, FSH, LH values, Bone age, difference between Chronological age and Bone age, Oestradiol/Testosterone, Uterine Length and Testicular Volume over time will be graphically presented via individual observed values (scatter) as well as mean and

standard deviation of the observed values (Baseline, Month 3, Month 6, Month 9 and Month 12).

5.7.3.3 Sensitivity Analysis

No sensitivity analysis will be performed.

5.7.3.4 Subgroup Analysis

No subgroup analyses will be performed.

5.8 Safety

5.8.1 General Consideration

All safety summaries and analyses will be based upon the Safety population. All safety data will be included in participant data listings (see listing detail conventions in Appendix A4). There will be no statistical comparison between the gender groups for safety data, unless otherwise specified within the relevant section.

If conversion factors are used, they should be presented either in the relevant section or a link to section 7 should be added.

All AEs will be recorded and graded according to the current version of the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0.

5.8.2 Extent of Exposure

Duration of exposure will be defined in days as:

Days of exposure = Date of Last Study Visit – First dose date + 1.

The following extent of exposure summaries will be presented:

- Summary of the duration of exposure to treatment, by gender group. Provide the mean, median, and the count and percentage of participants exposed for specified periods of time choosing appropriate time intervals.
- Summary of the actual dose by gender group. Provide the mean, median, and the count and percentage of participants exposed for specified periods of time choosing appropriate time intervals.
- Summary of number of injections,
- Summary of total exposure,
- Listing of exposure data.

5.8.3 Adverse Event

All adverse events (AEs) recorded in the eCRF will be coded using the latest version of MedDRA dictionary in effect within IPSEN at the time of the database lock.

A TEAE is defined as any AE that occurs during the active phase of the study if:

- It was not present prior to receiving the dose of triptorelin, or
- It was present prior to receiving the dose of triptorelin but the grade increased or became serious during the active phase of the study, or
- It was present prior to receiving the dose of triptorelin, the grade/seriousness is the same, but the causality changed to “related” during the active phase of the study
- Refer to appendix Partial/Missing Date Convention A2 for handling of partial date. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

Tabular summaries will be presented by gender group. Summaries will include the number and percentage of participants and classified by primary system organ class and preferred term. The following summaries will be reported for AEs, TEAE regardless of drug relationship, TEAE related to study drug, TEAE grade 3 and above regardless of drug relationship, TEAE grade 3 and above related to study drug, serious AEs (SAEs), AE leading to study drug discontinuation, and AE leading to death:

- An overview table summarizing the number and percentage of participants with at least one of the following AEs: any AE; any TEAE; SAE, treatment emergent SAE, treatment-related TEAE, treatment emergent-related SAE, Non-serious TEAEs, TEAE leading to treatment discontinuation; TEAE leading to discontinuation from the study, CTCAE Grade >=3 TEAE, Death, TEAE leading to death,
- A summary of the number and percentage of participants reporting a TEAE by gender group, SOC and PT,
- A summary of the number and percentage of participants reporting a TEAE by gender group and PT,
- A summary of the number and percentage of participants reporting a SAE by gender group and PT,
- A summary of the number and percentage of participants reporting a Serious TEAE by gender group and PT,
- A summary of the number and percentage of participants reporting a treatment related Serious TEAE by gender group and PT,
- A summary of the number and percentage of participants reporting a TEAE leading to treatment discontinuation by gender group and PT,
- A summary of non-serious TEAE by gender group, SOC and PT,
- A summary of the number and percentage of participants reporting a TEAE by gender group, CTCAE grade, SOC and PT,
- A summary of the number and percentage of participants reporting a drug-related TEAE by gender group, CTCAE grade, SOC and PT,
- A summary of the number and percentage of participants reporting a TEAE by gender group, causality, SOC and PT,
- A summary of the most common TEAEs by gender group, SOC and PT (reported by > 5% of participants in any gender group),

AEs summaries will be ordered in term of decreasing frequency for SOC and PT within SOC in the overall group and then similarly by decreasing frequency in the female group, and then alphabetically for SOC and PT within SOC. AEs summaries by PT will be ordered in term of decreasing frequency of PT in the overall group and then similarly by decreasing frequency in the female group, and then alphabetically for PT.

AEs will be counted as follows:

- Participants with more than one AE within a particular SOC are counted only once for that SOC. Similarly, participants with more than one AE within a particular PT are counted only once for that PT;

- Participants reporting a TEAE more than once within that SOC/ PT, the TEAE with the worst-case grade (grade order: 5>4>3>2>1>missing) will be used in the corresponding grade summaries;
- Participants reporting a TEAE more than once within that SOC/ PT, the TEAE with the worst-case relationship to study medication (order: related > not related > missing) will be used in the corresponding relationship summaries;
- If the CTCAE grade is missing for a TEAE, it will be considered as missing in the summary tables;
- Summary by CTCAE grade will be presented (in the same order as above);
- If the causality is missing for a TEAE, it will be considered related in the summary tables;
- The non-serious TEAEs table should include a specific row "any non-serious TEAE above 10%";
- A TEAE is counted only in the study where it started (if there is a change in the CTCAE grade, an additional AE should have been collected in the eCRF).

In addition, a listing with all AEs data will be listed by gender group including non-TEAEs, Treatment-emergence status will be flagged in the listing. Listing of Drug-related AEs will also be added.

The following listing will also be provided:

- A listing of all deaths that occurred during the study,
- A listing of all serious adverse events,
- A listing of all adverse events leading to discontinuation of study treatment.

Local tolerability Abnormalities

The following summary tables will be provided:

- A summary of the number and percentage of participants reporting a local tolerability reaction, by gender, SOC and PT,

The following listing will be provided:

- A listing of all local tolerability reactions that occurred during the study.

5.8.4 Laboratory Data

All laboratory data will be presented in the units of International System of Units (SI).

Describe the summaries that are to be provided. These may include the following summaries:

- A summary of the actual and change from baseline in each laboratory parameter by gender group and timepoint,
- A shift from baseline to worst post-dose (i.e. highest grade) in CTCAE Grade of laboratory results.

For shift tables, the denominator should be the number of participants with both a baseline and a post-baseline assessment at a given timepoint.

In addition, the following listings are to be provided:

- A listing of all laboratory data. Out-of-reference-range values will be flagged as high (H) or low (L),
- A listing of CTCAE grade 3 and higher values. All data for a laboratory parameter will be displayed for a participant who has any post-baseline value with CTCAE grade greater than or equal to 3 for the parameter.

5.8.5 Vital Signs

Describe the summaries that are to be provided. These include:

- A summary of the actual and change from baseline in each vital sign parameter (blood pressure and heart rate) by gender group and timepoint.

The following listing is to be provided:

- A listing of vital sign data by gender group, with abnormal value highlighted.

5.8.6 Electrocardiogram (ECG)

Not applicable.

5.8.7 Physical Examination

The following summary and listings will be provided:

- A shift from baseline (normal vs abnormal) to each post-baseline visit
- A listing of physical examination data,
- A listing with any participants with at least one physical examination abnormality.

5.8.8 Other (if applicable)

Participants are to be discontinued from the study if they become pregnant. Pregnancy data will be shown in a data listing if applicable. No special analysis will be performed on the pregnancy.

5.9 PK

The individual plasma triptorelin concentration are measured in all participants receiving study drug on Day 1 (to be taken predose and at 4 hours post-injection); at Month 3 visit; at Month 6 visit (to be taken predose of second injection, and at 4 hours post-injection); and Month 12 EOS/early withdrawal visit. Individual listings and descriptive summary statistics will be presented for triptorelin plasma concentrations.

Descriptive statistics (n, mean, SD, SEM, %CV, 95% lower CI, 95% upper CI, median, minimum and maximum, geometric mean, geometric SD, geometric CV%, 95% Lower Geomean CI, 95% upper Geomean CI) will be summarized by each scheduled visit, and by timepoint where applicable for triptorelin plasma concentrations. To compute descriptive statistics, all BLQ values must be replaced by missing in the data set. BLQ values substituted by missing are excluded in the calculation of descriptive statistics.

Triptorelin concentrations will be displayed with the same precision as the BLQ values. For the descriptive statistics, calculations derived from concentrations (mean, min, max, median, SD etc.) will follow the same rule as Min and Max, but coefficient of variation (CV%) will be displayed with one decimal digit only.

The descriptive statistics should be displayed by visit/time point, only if at least 2/3 (2 out of every 3 values) of the data are available and above the limit of quantification. Otherwise, only

minimum and maximum are reported. Individual and mean plasma concentration time profiles, as well as spaghetti plots, on the PK Set will be generated.

If required and warranted by the data, an attempt to build a model to characterize the PK in the population will be made. This will be described in a separate analysis plan and the outcomes summarised in a standalone report.

5.10 Anti-drug Antibodies (if applicable)

Not applicable.

5.11 Pharmacodynamics (if applicable)

Not applicable.

6 DATA HANDLING

6.1 Visit Window

All data will be organized and analysed according to the scheduled visits outlined in the protocol. As defined by the protocol, Visit 1 (Screening visit) has to be performed within Day -28 to Day -1 prior to first treatment. Visit 2 (Day 1) will be the day of first treatment. Visit 3 (Month 3) will correspond to Day 82 to Day 88. Visit 4 (Month 6) will correspond to Day 166 to Day 172. Visit 5 (Month 9) will correspond to Day 250 to Day 256 and Visit 6 (Month 12) will correspond to Day 337 to Day 344.

Participants who complete the study will perform final procedures and assessments at the final visit (Month 12). Participants who withdraw from the study before the completion of the evaluation period will be invited to attend an Early Withdrawal visit to perform early discontinuation procedures and assessments.

For participants who do not have a final visit within 6 months after their last triptorelin dose, efficacy evaluations (including PK sampling) will not be performed. Data from any efficacy evaluations performed after this time will not be collected on the eCRF.

6.2 Unscheduled Visits, Retest, Withdrawal Visit,

All listings will include retests and unscheduled visits, while for the description by visit in the tables, only the scheduled visits according to the protocol will be described.

Unscheduled visit and retest measurements will be used to provide a measurement for a baseline data or endpoint value (e.g. worst value), if appropriate according to their definition. These measurements will also be used to determine abnormal laboratory, vital signs values or ECG.

If a value requires a retest (for laboratory values and vital signs) the closest non-missing reliable value to the scheduled visit will be used in the summary tables.

Participants who have withdrawn early from the study have their last assessment entered as visit 90 in the eCRF.

7 DERIVED DATA (IF APPLICABLE)

When applicable, below derivation rules should be followed:

- **Change from baseline**

Change from baseline at a given visit will be calculated as a difference from baseline.

- **Chronological Age**

Chronological Age (years) will be calculated as follows and keep two decimals for the calculated result:

Chronological Age = (Visit Date - birth date + 1)/365.25.

- **BMI**

BMI (kg/m2) will be derived as Weight (kg)/[Height(cm)/100]**2 measured at each visit and rounded to the nearest decimal.

- **Bone Age**

For bone age recorded as m+, n- or m-n, the original result will be listed in listing. And for m+, we will use m+0.25 in the summary analysis, for n-, we will use n-0.25 in the summary analysis, for m-n, we will use middle point between m and n in the summary analysis. For examples, 9+ will be updated to 9.25, 8- will be updated to 7.75 and 9-10 will be updated to 9.5. There is one exception, 8.8+ will be updated to 8.825 in the summary analysis.

- **Growth Velocity**

For growth velocity recorded as m-n, the original result will be listed in listing and we will take the middle point between m and n in the summary analysis. For example, 7-8, will be updated to 7.5 in the summary analysis.

- **Oestradiol and Testosterone**

For oestradiol and testosterone recorded as <17.936 or <11.981, the original result will be listed in listing and update <17.936 to 17.936, <11.981 to 11.981 in the summary analysis.

8 REFERENCES

Reference to ICH regulatory guidelines:

- ICH E3: Structure and Content of Clinical Study Reports
- ICH E6 (R2): Good Clinical Practice
- ICH E9: Statistical Principles for Clinical Trials
- ICH E9 (R1) Addendum: Estimands and Sensitivity Analysis in Clinical Trials

Reference to European Medicines Agency (EMA) or point to consider guidelines:

- Adjustment for baseline covariates in clinical trials
- Choice of a non-inferiority margin
- Clinical trials in small populations
- Data monitoring committees
- Investigation of subgroups in confirmatory clinical trials
- Missing data in confirmatory clinical trials
- Application with Meta Analyses, One pivotal study
- Multiplicity issues in clinical trials

Switching between superiority and non-inferiority

Reference to Food and Drug Administration (FDA) guidelines:

- Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

Reference to NMPA regularoty guidelines:

- Biostatistics Guidelines for Drug Clinical Trials
- Good Clinical Practice
- Guidelines for Principles of Structure and Content of Clinical Study Report of Drugs

- Guidelines for Data Management and Statistical Analysis Plan and Report of Drug Clinical Trials

Standard Ipsen SDTM user guide
Standard ADaMs user guide

Ipsen Global Style guide

9 APPENDICES

A2.Partial/Missing Date Convention

In all listings, missing or incomplete dates should be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following methods will be used:

- The most conservative approach will be systematically considered (i.e. if the onset date of an AE/concomitant medication is missing / partial, it is assumed to have occurred during the study treatment phase (i.e. a TEAE for AEs) except if the partial onset date or the stop date indicates differently.
- Where this is possible, the derivations based on a partial date will be presented as superior inequalities (i.e.: for an AE started in FEB2004 after the first IMP administration performed on 31JAN2004, the days since last dose will be "≥2", similarly the duration of ongoing AEs or medication will be "≥xx" according to the start and last visit dates).

Algorithm for Prior/ Concomitant

Medication, non-drug therapies and surgical procedures start and stop dates will be compared to the date of the first IMP administration to allow classification as either Prior only, Prior and Concomitant, or Concomitant only.

In case of partial start and/or stop medication/ non-drug therapies/surgical procedures dates, imputation will be done to determine the classification:

- If a partial start date, the first day of the month will be imputed for missing day and January for missing month,
- If a partial stop date, the last day of the month will be imputed for missing days and December will be imputed for missing month.

In case incomplete start or stop date does not allow the classification, will be classified as concomitant.

For studies with injection cycles:

If the start date of a medication is partial or missing, the medication will be assigned to the most recent treatment received on or before the medication start date (taking into account date stopped).

Algorithm for TEAE

For deriving the TEAE flag the following process of temporary date imputation is done (for AE start date only assuming no AE end date are missing). The date imputation algorithm for incomplete adverse event start dates is described in Table 2. Classification of adverse event according to its treatment-emergent status is then done using the imputed date.

In the following table, all dates are presented using an YYYY-MM-DD format. As an example, suppose First IMP administration = 2002-08-11 and several AEs have incomplete start dates.

Table 2: Data imputation algorithm for AE start date

Description of incomplete date	Imputed numeric date	Example	
		Character date	Imputed date
Day is missing			
YYYY-MM < YYYY-MM of [First IMP admin.]	YYYY-MM-01	2002-07-XX	2002-07-01
YYYY-MM = YYYY-MM of [First IMP admin.]	Min ([First IMP admin.], AE end date)	2002-08-XX	Min (2002-08-11, AE end date)
YYYY-MM > YYYY-MM of [First IMP admin.]	YYYY-MM-01	2002-09-XX	2002-09-01
Day and month are missing			
YYYY < YYYY OF [First IMP admin.]	YYYY-01-01	2001-XX-XX	2001-01-01
YYYY = YYYY OF [First IMP admin.]	Min ([First IMP admin.], AE end date)	2002-XX-XX	Min (2002-08-11, AE end date)
YYYY > YYYY OF [First IMP admin.]	YYYY-01-01	2003-XX-XX	2003-01-01
Day, month, and year are missing			
XXXX-XX-XX	Min ([First IMP admin.], AE end date)		Min (2002-08-11, AE end date)

YYYY = non-missing year, MM = non-missing month, DD = non-missing day, XX = missing field.

For studies with injection cycle:

If an AE onset date is partial or missing, the event will be allocated to the first IMP administration where onset could have occurred (taking into account date and time stopped).

If AE end date is partial, imputation could be done assuming the latest possible date (i.e. last day of month if day unknown, or 31st of December if day and month are unknown).

A3. Programming Convention for Outputs

All text fields must be left justified and numeric or numeric with some text specification (e.g.: not done, unknown, <4.5, …) must be decimal justified.

The mean, median, lower quartile, upper quartile, SD and standard errors (SE) of the mean, 95% confidence interval values will be reported to one decimal place greater than the raw data recorded in the database.

The minimum and maximum values will be reported with the same number of decimal places as the raw data recorded in the database.

In general, the maximum number of decimal places reported should be four for any summary statistic.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentage will be calculated using n as denominator. The denominator n will be specified in a footnote for clarification if necessary. If sample sizes are small, the data displays will show the percentages, but in the CSR only frequency counts should be described.

P-values will be reported to four decimal places (e.g.: p=0.0037), after rounding. P-values which are less than 0.0001 will be presented as '<0.0001'.

All values below or above a limit of detection (e.g. <0.1 or >100) will be listed as such.

Dates will be presented in the format [ddmmmyyyy] and times in the format [hh:mm].

A4. Listings Conventions

Any listings will contain at least the following data: participant identifier, age and gender. When dates are presented, the associated study days should be included. They should be sorted by gender group then participant identifier. For multicentre studies, listings should be broken down by centre and gender group.

Note: In this study (D-CN-52014-244), any listings will contain at least the following data: participant identifier, age and gender. All listings should be sorted by participant identifier.

A5. Z-score and Percentile for Height for Age

The external file (CDCref_d.xls) from Division of Nutrition, Physical Activity, and Obesity of American CDC contains the L, M, and S parameters needed to generate exact percentiles and z-scores along with the percentile values for the 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, and 97th percentiles by sex (1=male; 2=female) and single month of age. Age is listed as interval in the external file; for example, _AGEMOS1=8.5, _AGEMOS2=9.5 months represents 8.5-9.4999 months. To obtain L, M, and S values at finer age or length/stature intervals interpolation could be used.

The LMS parameters are the median (M), the generalized coefficient of variation (S), and the power in the Box-Cox transformation (L). To obtain the value (X) of a given physical measurement at a particular z-score or percentile, use the following equation:

$$X = M\,(1 + LSZ)^{**}(1/L),\ L \neq 0$$

Or

$$X = M \exp(SZ),\ L = 0$$

where the L, M, and S are the values from the appropriate table corresponding to the age in months of the child (** indicates an exponent, such that M(1+LSZ)**(1/L) means raising (1+LSZ) to the (1/L)th power and then multiplying the M; exp(X) is the exponentiation function, e to the power X). Z is the z-score that corresponds to the percentile. z-scores correspond exactly to percentiles, e.g., z-scores of -1.881, -1.645, -1.282, -0.674, 0, 0.674, 1.036, 1.282, 1.645, and 1.881 correspond to the 3rd, 5th, 10th, 25th, 50th, 75th, 85th, 90th, 95th, and 97th percentiles, respectively.

The LMS parameters need to be adjusted based on actual age (age), use the following equation:

ageint = CDCref_d._agemos2- CDCref_d._agemos1;
dage= age - CDCref_d._agemos1;
L=CDCref_d._LLG1+ (dage*(CDCref_d._LLG2- CDCref_d._LLG1))/ageint;
M=CDCref_d._MLG1+ (dage*(CDCref_d._MLG2- CDCref_d._MLG1))/ageint;
S=CDCref_d._SLG1+ (dage*(CDCref_d._SLG2- CDCref_d._SLG1))/ageint;

To obtain the z-score (Z) and corresponding percentile for a given measurement (X), use the following equation:

$$Z = \frac{((X/M)^{**}L) - 1}{LS},\ L \neq 0$$

or

$$Z = \ln(X/M)/S,\ L = 0$$

where X is the physical measurement (e.g. weight, length, head circumference, stature or calculated BMI value) and L, M and S are the values from the appropriate table corresponding to the age in months of the child (or length/stature). (X/M)**L means raising the quantity (X/M) to the Lth power.

For example, to obtain the 5th percentile of height-for-age for a 9-month-old male, we would look up the L, M and S values from the CDCref_d table, which are _LLG1=-1.29571459, _MLG1=70.94803912, _SLG1=0.038546833, ._LLG2=-1.177919048, _MLG2=72.34586111, _SLG2=0.038526262.

After adjustment by age, L, M, S would be -1.236816819, 71.646950115, and 0.0385365475, respectively. Using the equation above, we calculate that the z-score for this child is 1.15. This z-score corresponds to the 88th percentile.

CCI