STATISTICAL ANALYSIS PLAN

AN OPEN-LABEL, MULTICENTRE, SINGLE-ARM STUDY TO ASSESS THE EFFICACY AND SAFETY OF TRIPTORELIN 3-MONTH FORMULATION IN CHINESE CHILDREN WITH CENTRAL PRECOCIOUS PUBERTY

STUDY NUMBER: D-CN-52014-243

This statistical analysis plan is based on:
PROTOCOL VERSION AND DATE: 3.0 – 16 MARCH 2021

SAP Version	Date
Final Version 1.0	24MARCH2021
Final Version 2.0	20MAY2021
Final Version 2.1	09MAR2022

APPROVAL PAGE

STUDY NUMBER:	D-CN-52014-243
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SAP VERSION:	Final Version 2.1
SAP DATE:	09 Mar 2022

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	24 March 2021	Not Applicable
2.0	20 May 2021	Protocol updated from version 2 to version 3
2.1	05Mar2022	1. Remove PCSA part; 2. Add details to handle "bone age recorded as 9+ or 10-" in section 7; 3. Add details to handle "laboratory values below LLOQ or above ULOQ" in section 5.1. 4. Update 5.7.2.1 by removing "estimand" section.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	Wording Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Transaminase
ATC	Anatomic Therapeutic Class
BA	Bone Age
BMI	Body Mass Index
CA	Chronological Age
CI	Confidence Interval
CRF	Case Report Form
CPP	Central Precocious Puberty
CRO	Clinical Research Organisation
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
e	Electronic
EOS	End of Study
FDA	Food and Drug Administration
FSH	Follicle-stimulating Hormone
GnRH	Gonadotropin-releasing Hormone
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ITT	Intention-To-Treat
IU	International Units
i.v.	Intravenous
LH	Luteinising Hormone
LLN	Lower Limit of Normal
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
PASS	Power Analysis and Sample Size
PD	Pharmacodynamics

ABBREVIATION	Wording Definition
PK	Pharmacokinetic
PN	Preferred Name
PPS	Per protocol set
PR	Prolonged Release
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System®
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SI	Standard International
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures and Listings
ULN	Upper Limit of Normal
WHO-DD	World Health Organization – Drug dictionary

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-52014-243. 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 ICH E3).

2 PROTOCOL OVERVIEW

2.1 Study Objectives and Hypotheses

2.1.1 Objectives of the Main study phase

2.1.1.1 Primary objective

The primary objective of the study is to assess the efficacy of the triptorelin 3-month prolonged release (PR) formulation in suppressing luteinising hormone (LH) levels to pre-pubertal levels (defined as a peak LH ≤3 IU/L after intravenous (i.v.) gonadotropin-releasing hormone (GnRH) stimulation) at Month 3 in Chinese children with central precocious puberty (CPP).

2.1.1.2 Secondary Objectives

The secondary objectives of the study are as follows:

- To assess the efficacy in suppressed LH response to GnRH test at Month 6
- To assess follicle-stimulating hormone (FSH) response to GnRH test at Month 3 and Month 6
- To assess LH and FSH levels at Month 3 and Month 6
- To assess sex hormone serum concentrations (oestradiol for girls and testosterone for boys) at Month 3 and Month 6
- To assess sexual maturation (pubertal stage as per Tanner method) at Month 6
- To assess auxological parameters including height, growth velocity, weight and body mass index (BMI) at Month 3 and Month 6
- To assess bone age (BA), the difference between BA and chronological age (CA) at Month 6
- To assess gonadal development as determined by uterine length in girls and testicular volume in boys at Month 6
- To assess the safety profile.

2.1.1.3 Exploratory Objective

- To assess plasma triptorelin levels at Day 1, Month 3 and Month 6.

2.1.2 Objectives of the Extension Phase

To describe the long-term efficacy and safety of Triptorelin 3-month prolonged release formulation through following objectives:

- To assess the percentage of subjects with suppressed LH hormones at Month 12
- To assess LH and FSH levels at Month 9 and 12
- To assess sex hormone serum concentrations (oestradiol for girls and testosterone for boys) at Month 9 and 12
- To assess sexual maturation (pubertal stage as per Tanner method) at Month 12
- To assess auxological parameters including height, growth velocity, weight and body mass index (BMI) at Month 9 and Month 12
- To assess bone age (BA), the difference between BA and chronological age (CA) at Month 12
- To assess gonadal development as determined by uterine length in girls and testicular volume in boys at Month 12
- To assess the safety profile.

2.1.3 Study Hypothesis

The effectiveness of triptorelin 3-month formulation in Chinese population of CPP children has the same or similar trend with that in overseas CPP population.

2.2 Overall Study Design and Investigational Plan

The study is a prospective, open-label, multicentre, single-arm, interventional study intended to evaluate the efficacy and safety of triptorelin 3-month formulation in Chinese children with CPP.

Main study phase:

A total of 32 participants, including three boys, will be enrolled in the study and treated with an intramuscular (i.m.) injection of triptorelin on Day 1 of the study and at Month 3 (3 months after the first injection). Triptorelin injections do not have to be adapted based on body weight but the participant should have a minimum weight of 20 kg.

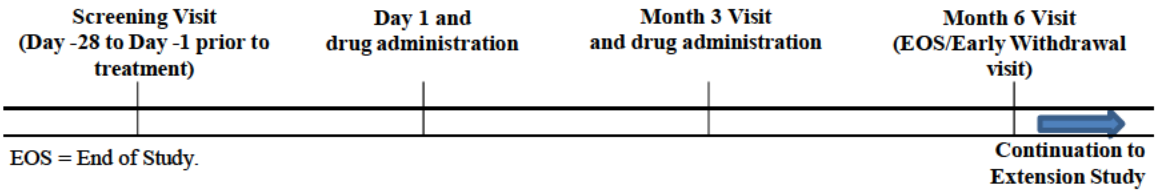
The study consists of a Screening period (the Screening visit will take place up to 28 days before enrolment), during which participants with CPP will be screened for eligibility before receiving the first triptorelin injection (Day 1 of the study) and will visit the study centre at Month 3 and Month 6 for efficacy and safety assessments (Figure 1). Participants will receive a total of two injections during the study period before they attend the End of Study (EOS) visit at Month 6.

Each participant is expected to be enrolled in this study for a minimum of 6 months and up to 7 months (including Screening period).

Participants who complete the study will perform final procedures and assessments at the final visit (Month 6). 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 main study design is described in the following study flow chart.

Figure 1 Main Study Design



EOS = End of Study.

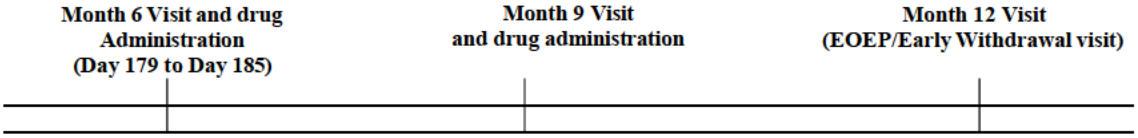
Extension phase:

The extension of the study will provide the possibility for subjects to continue with their study drug treatment, per investigators decision, for an additional 6 months. This will imply a triptorelin injection at Month 6 and an additional triptorelin injection at Month 9, before they attend the End of Extension Phase (EOEP) visit at Month 12. This Extension phase i s optional.

Each participant may be treated with the study drug for up to 12 months.

The Extension study design is described in the following study flow chart.

Figure 2 Extension Study Design



EOEP = End of Extension Phase.

2.3 Sample Size Determination and Power

Main study phase:

The purpose of this study is to observe whether the effectiveness of triptorelin 3-month formulation in Chinese population of CPP children has the same or similar trend with that in overseas CPP population, mainly using descriptive statistical analysis. Although no formal statistical testing will be carried out, the following assumptions were made, based on global pivotal study 2-54-52014-143 [Zenaty 2016], for the sample size to enable an evaluation of the trend of effectiveness:

- Expected outcome for the proportion of children with a suppressed LH response to the GnRH stimulation test (stimulated peak LH ≤3 IU/L) at Month 3 is 90%
- Null proportion is 70%
- An exact binomial test of a proportion with a one-sided nominal significance level of 0.05 and power =85%
- Expected common dropout rate =10%.

Under these assumptions, approximately 32 (28 with additional 10% dropouts) participants (Power Analysis and Sample Size (PASS) software) including three boys are planned to be

enrolled into the study in order to observe the efficacy of the triptorelin 3-month formulation in the proportion of children with a suppressed LH response to the GnRH stimulation test at Month 3.

Extension phase:

The number of participants included in the extension study will be dependent on the number of participants from study D-CN-52014-243 who give consent to continue into the extension study. A maximum of 32 participants will be expected to be enrolled in the extension phase.

2.4 Randomization and Blinding (if applicable)

This is a non-randomised, open-label study.

2.5 Schedule of Assessments

Schedule of assessments is presented in section 5.1 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 DMC will be used in this study.

3.2 Interim Analysis / Other Analyses

No interim analysis will be performed. Three analyses are planned according to the following data cut-offs if applicable:

(1) The first analysis will be performed when all participants have completed the first 3 months of the study period. The cut-off date considered for this analysis will be the date of the last Month 3 visit for the last participant. All available data at the time of this data cut-off date will be included in this analysis. The purpose of this analysis will be the final analysis of the primary efficacy endpoint, as well as the secondary efficacy and safety analyses of the first 3 months of the study period. This analysis will not be considered as an interim analysis because the first 3 months of the study period is of primary interest.

(2) The second analysis will be performed when all participants have had the opportunity to complete the main study (Month 6). This reporting database will include all main study data for all participants enrolled into the study.

3.3 Final Analysis

Final analysis will be done when all participants complete the extension phase and after database lock.

4 ANALYSIS POPULATIONS (SETS)

The following populations will be used during statistical analyses:

- **Screened population**: All participants screened (i.e. who signed the informed consent)
- **Safety population**: All participants who received at least one dose of study medication and have at least one post-baseline safety assessment
- **Intention-To-Treat population** (ITT): All participants who received at least one dose of study medication
- **Modified Intention-To-Treat population** (mITT): All treated participants having at least one baseline and at Month 3 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 received at least one dose of study medication and have at least one valid and quantifiable concentration in main study phase.

4.1 Populations Analysed

Main study phase

The primary efficacy analysis will be performed on the mITT population. Supportive analysis of the primary efficacy endpoints will be based on the ITT and the PP populations.

The secondary efficacy analyses will be based on the mITT population. Supportive analysis of the secondary analyses may be performed on the PP population.

The analyses of safety data will be performed based on the Safety population.

The analyses of PK data will be performed based on the PK population.

Extension phase

The analysis sets for the efficacy endpoints will be the ITT set and the PP set. Analyses and summary tables for the safety endpoints will be based upon the Safety population.

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 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

TFLs will be displayed using the following gender group label: Female, Male, Overall.

5.1.1.3 Presentation of Visits / Timepoints

Summaries by visit will be presented using visit number as collected in the eCRF.

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

Long Visit Name	Short Name
Screening (Visit 1)	Scr
Baseline (Visit 1)/ Baseline (Visit 2)	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, standard deviation (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 Population

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 for main study phase with the number and percentage of participants screened, screen failed, reason for screen failures, treated, completed the main study

phase, withdrawn the main study and reason for withdrawal and extension phase with the number and percentage of participants enrolled, treated, completed the extension phase, withdrawn the extension phase 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 separately in main study phase and extension phase,
- Listing of dates of visit including duration of participant participation for the treated participants on the ITT population,
- Listing of screen failure participants on 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 protocol deviations by deviation category separately in main study phase and extension phase (see DV section of Standard SDTM+ user guide),
- All protocol deviations will be listed with flags indicating if deviations are major or minor PDs separately in main study phase and extension phase,
- A separate listing for major protocol deviations will be displayed separately in main study phase and extension phase,

5.4 Demography and Other baseline characteristics

All demographic and baseline characteristics summaries and listings will be provided for ITT, mITT, PPS and safety population.

Following summaries will be provided on:

- Demographic variables (age, ethnicity, sex)
- Other baseline characteristics (height, weight, BMI, pubertal stage, growth velocity, bone age, chronological age, the difference between bone age and chronological age),

- Baseline Disease characteristics (Time from initial diagnosis of CPP, GnRH-stimulated LH peak, GnRH-stimulated FSH peak, Basal LH, 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 separately in main study phase and extension phase.

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 MedDRA in effect within IPSEN at the time of database lock. Medications will be coded using the latest version of WHO-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 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 Name PN,
- Concomitant medications (PC, C) for the study indication by ATC class (ATC level 2) and preferred Name PN,
- 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 3-month formulation), medroxyprogesterone acetate, growth hormone or IGF-1, systemic or inhaled steroids (mild topical steroids are permitted), anticoagulants (heparin and coumarine derivatives).

5.6 Compliance

Compliance will be present separately in main study phase and extension phase,

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 (Main Study Phase)

5.7.1 General Considerations

The analysis sets for the primary and secondary efficacy endpoints will be the mITT population.

Supportive analysis of the primary efficacy endpoints will be based on the ITT and the PPS populations. Supportive analysis of the secondary analyses may be performed on the PPS 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

The statistical analysis of efficacy is only descriptive therefore no formal statistical significance testing will be performed.

5.7.1.2 Statistical/analytical issues

Adjustments for Country/Centre Effect

Descriptive analysis will be carried out to evaluate any possible centre effect.

Handling of Dropouts or Missing Data

A NRI method will be used for missing LH response and FSH response at month 3 or month 6. For any missing value of LH response and FSH response at month 3 or month 6, a Non-response value will be imputed.

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

Since no formal hypothesis test will be performed in this study, no multiple testing will be performed in this study

Use of an "Efficacy Subset" of Participants

No Efficacy subset is planned in this study.

Examination of Subgroups

No subgroup analysis is planned.

5.7.2 Analysis of Primary Efficacy Endpoint

5.7.2.1 Endpoint

LH Response: defined as a peak LH ≤3 IU/L after intravenous (i.v.) gonadotropin-releasing hormone (GnRH) stimulation) in Chinese children with central precocious puberty (CPP).

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 90% confidence interval (CI) for a binomial proportion will be computed by SAS® using the exact binomial distributions on the mITT.

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 for study discontinuation and the timing of 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 analyses will be conducted to further explore the primary efficacy endpoint with the same statistical method using NRI method on the ITT set.

A PPS population will also be used to explore the primary efficacy endpoint with the same statistical method.

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, Treatment Effect and Estimand Definition

Secondary efficacy endpoints and evaluations are summarised in following table:

Table 1 Secondary Efficacy Endpoints and Evaluations

Measure	Timepoint	Variable	Endpoint
Basal LH and FSH	Baseline, Month 3 and Month 6 (EOS)	LH and FSH concentration	Change in basal serum LH and FSH levels at Month 3 and Month 6 compared to baseline
Peak LH after GnRH	Baseline, Month 3 and	Peak LH levels after	Change in peak LH levels after GnRH stimulation test at

stimulation test	Month 6 (EOS)	GnRH stimulation (30, 60 and 90 minutes)	Month 3 and Month 6 compared to baseline; Proportion of children with LH suppression defined as stimulated peak LH ≤3 IU/L after GnRH stimulation at Month 6.
Peak FSH levels after GnRH stimulation test	Baseline, Month 3 and Month 6 (EOS)	Peak FSH levels after GnRH stimulation (30, 60 and 90 minutes)	Change in peak FSH levels after GnRH stimulation test at Month 3 and Month 6 compared to baseline.
E2 and testosterone serum concentrations	Baseline, Month 3 and Month 6 (EOS)	Sex steroids levels	Proportion of children with sex steroids suppressed within prepubertal ranges (E2 ≤20 pg/mL in girls and testosterone ≤0.3 ng/mL in boys); Change in sex steroids levels compared to baseline
Pubertal stage (Tanner Method)	Baseline, Month 6 (EOS)	Pubertal stage	Change in pubertal stage (genital stage in boys, breast stage in girls and pubic hair stage in both sexes) compared to baseline; Proportion of children with stabilised pubertal stage compared to baseline
Auxological parameters (height, growth velocity, weight, BMI)	Baseline, Month 3 and Month 6 (EOS)	-	Change in auxological parameters compared to baseline
BA	Baseline, Month 6 (EOS)	-	Change in BA, difference between BA and CA compared to baseline
Uterine/ovary or testis volume	Baseline, Month 6 (EOS)	Gonad development	Change in uterine length in girls and testicular volume in boys compared to baseline

BA = Bone age; BMI = Body mass index; CA = Chronological age; E_2 = Oestradiol; EOS = End of Study; FSH = Follicle-stimulating hormone; GnRH = Gonadotropin-releasing hormone; LH = Luteinising hormone.

5.7.3.2 Secondary Analysis

For secondary efficacy endpoints related to a change at Month 3, 6 compared to baseline, the descriptive summary statistics (number of participants (n), mean, SD, median, quartiles, minimum, maximum) will be calculated on the mITT.

Exact two-sided 90% CI will also be constructed for all secondary endpoints expressed as proportions.

GV cm/y, Height, Weight, BMI, FSH, LH values, Bone age, difference between Chronological age and Bone age, mean 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, and Month 6).

5.7.3.3 Sensitivity Analysis

Secondary efficacy endpoints will be performed on the PPS using the same statistical method as mITT.

5.7.3.4 Subgroup Analysis

No subgroup analyses will be performed.

5.8 Safety (Main Phase)

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. 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. Provide the mean, median, sum and the count and percentage of participants exposed to specified dose levels choosing appropriate dose 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. AEs will be classified as treatment-emergent AEs (TEAEs) according to the rules below:

- Events with start date on or after the date of first IMP administration and up to the EOS or 185 days after first dose days which comes first.
- Events whose CTCAE grade worsens on or after the date of first IMP administration,
- Events whose causality changes to "Related" on or after the date of first IMP administration,
- Refer to appendixPartial/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. 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, SOC 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 TEAE by gender group 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 most frequent AEs (reported in > 5%) by gender group, SOC and PT.

AEs summaries will be ordered in term of decreasing frequency for SOC and PT within SOC in the gender, and then alphabetically for SOC and PT within SOC.

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 CTCAE grade will be used in the corresponding CTCAE grade summaries;
- Participants reporting a TEAE more than once within that SOC/ PT, the TEAE with the worst case relationship to study medication 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;
- 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 summary of the number and percentage of participants experiencing treatment-emergent clinically significant laboratory abnormalities, by gender group and laboratory parameter,
- 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 by gender group and timepoint,

5.8.6 Electrocardiogram (ECG)

Not applicable.

5.8.7 Physical Examination

Physical examinations, including body weight (kg) and body height (cm), will be conducted at Baseline (Visit 2), at Visit 3 and at Visit 4 if applicable.

The following summary and listings will be provided:

- A shift from baseline (normal vs abnormal) to each post-baseline visit
- A change from baseline 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 Efficacy and Safety Evaluations (Extension Phase)

An additional analysis on efficacy and safety endpoints will be performed considering the extension phase duration, a period of an additional 6 months, lasting until the End of Extension Phase Visit at Month 12.

As this is an extension phase following the main study phase, the efficacy and safety endpoints in the extension phase will be summarised descriptively. No formal statistical hypotheses testing will be performed.

Statistical analyses will include the following:

- For the continuous endpoints, the descriptive summary statistics (number of participants (n), mean, SD, median, minimum, maximum) will be calculated
- For the categorical endpoints, the summary statistics of number and percentage of participants and the exact two-sided 90% confidence interval (CI) will be calculated.

5.9.1 Efficacy Endpoint for Extension Phase

The extension phase efficacy endpoints are the following:

Table 2 Efficacy Endpoints and Evaluations of extension phase

Measure	Timepoint	Variable	Endpoint
Basal LH and FSH serum levels	Baseline, Month 9 and Month 12 (EOEP)	LH and FSH concentration	Change in basal serum LH and FSH levels at Month 9 and Month 12 compared to baseline
Peak LH after GnRH stimulation test	Baseline and Month 12 (EOEP)	Peak LH levels after GnRH stimulation (30, 60 and 90 minutes)	Change in peak LH levels after GnRH stimulation test at Month 12 compared to baseline; Proportion of children with LH suppression defined as stimulated peak LH <=3 IU/L after GnRH stimulation at Month 12.
Peak FSH levels after GnRH stimulation test	Baseline and Month 12 (EOEP)	Peak FSH levels after GnRH stimulation (30, 60 and 90 minutes)	Change in peak FSH levels after GnRH stimulation test at Month 12 compared to baseline.
E2 and testosterone serum concentrations	Baseline, Month 9 and Month 12 (EOEP)	Sex steroids levels	Proportion of children with sex steroids suppressed within prepubertal ranges (E2 <=20 pg/mL in girls and testosterone <=0.3 ng/mL in boys); Change in sex steroids levels compared to baseline
Pubertal stage (Tanner Method)	Baseline, Month 12 (EOEP)	Pubertal stage	Change in pubertal stage (genital stage in boys, breast stage in girls and pubic hair stage in both sexes) compared to baseline; Proportion of children with stabilised pubertal stage compared to baseline

Auxological parameters (height, growth velocity, weight, BMI)	Baseline, Month 9 and Month 12 (EOEP)	-	Change in auxological parameters compared to baseline
BA	Baseline, Month 12 (EOEP)	-	Change in BA, difference between BA and CA compared to baseline
Uterine length or testis volume	Baseline, Month 12 (EOEP)	Gonad development	Change in uterine length in girls and testicular volume in boys compared to baseline

BA = Bone age; BMI = Body mass index; CA = Chronological age; EOEP = End of Extension Phase; FSH = Follicle stimulating hormone; GnRH = Gonadotropin-releasing hormone; LH = Luteinising hormone; E2 = Oestradiol.

Unless otherwise specified, all analysis of extension phase efficacy endpoints will be the same as main study phase.
For extension phase efficacy endpoints related to a change at Month 9 and Month 12 compared to baseline, the descriptive summary statistics (n, mean, SD, median, minimum, maximum) will be calculated on the ITT and PP. Exact two-sided 90% CIs will also be constructed for all extension phase efficacy endpoints expressed as percentages.

5.9.2 Safety Endpoint for Extension Phase

The extension phase safety endpoints are the following;

- Incidence of treatment-emergent adverse events (TEAEs) throughout the study, including local tolerability
- Change in clinical safety laboratory (blood biochemistry, haematology and urinalysis) parameters at Months 9 and 12
- Change in physical examination and vital signs (blood pressure and heart rate) measurements at each visit

Unless otherwise specified, all the analysis of extension phase safety endpoints including AE, laboratory, physical examination and vital signs will be the same as main study phase.

5.10 Pharmacokinetics

Pharmacokinetics analysis is only for main study phase.
The individual plasma triptorelin concentration are measured in all subjects receiving study drug on Day 1 (to be taken predose and at 4 hours post-injection); at Month 3 visit (to be taken predose); and Month 6 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. 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.

5.11 Anti-drug Antibodies (if applicable)

Not applicable.

5.12 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 (Baseline visit) will be the day of first treatment. Visit 3 will correspond to Day 88 to Day 94 and participants who complete the study will perform final procedures and assessments at the final visit (Month 6).

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 3 months (i.e. up to Day 182±3 days as in Protocol Table 1) after their last triptorelin dose, efficacy evaluations should 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 electronic Case Report Form (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.

- **Age**

Age (years) will be calculated as follows and truncated to the largest integer that is less than or equal to the calculated result:

Age = (informed consent date of main study phase - birth date + 1)/365.25.

- **Chronological Age**

Chronological Age (years) will be calculated as follows and truncated to the largest integer that is less than or equal to 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 9+ or 10-, the original result will be listed in listing and update 9+ to 9.25 and 10- to 9.75 in the summary analysis.

8 REFERENCES

Zenaty D, Blumberg J, Liyanage N et al. A 6-Month Trial of the Efficacy and Safety of Triptorelin Pamoate (11.25 mg) Every 3 Months in Children with Precocious Puberty: A Retrospective Comparison with Triptorelin Acetate. Horm Res Paediatr 2016;86:188-95.

Reference to ICH regulatory guidelines:

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

Reference to 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 FDA guidelines:

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

Standard SDTM+ user guide

Ipsen Global Style guide

9 APPENDICES

CCI

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.

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 1. 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 1: Data imputation algorithm for AE start date (AESTDT)

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.

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 of the mean (SE), 90% 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 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 frequencies 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-52014-243), any listings will contain at least the following data: participant identifier, age and gender. All listings should be sorted by participant identifier.