1.0 Title Page

Statistical Analysis Plan for Study M16-904

A Phase 3, Multi-Center, Open-Label, Two-Part Study to Evaluate the Safety, Efficacy, Pharmacokinetics and Pharmacodynamics of Leuprolide Acetate 45 mg 6-Month Depot Formulation in Children with Central Precocious Puberty

Date: 21 December 2021

Version 4.0

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3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analysis to be completed by AbbVie Clinical Statistics Department for leuprolide acetate Study M16-904.

The SAP will provide details to further elaborate statistical methods as outlined in the protocol and will describe analysis conventions to guide the statistical programming work. Unless noted otherwise, all analyses will be performed using SAS version 9.4 or later (SAS Institute Inc., Cary, NC 27513) under the UNIX operating system.

4.0 Study Background

4.1 Objective

Primary objective:

- To assess the safety and efficacy of LA 45 mg 6-month depot formulation for the treatment of CPP in children who are either naïve to treatment with a GnRHa or who have been previously treated with a GnRHa.

Secondary objective:

- To evaluate the pharmacokinetic profile and pharmacodynamics of leuprolide following intramuscular administration of the LA 45 mg 6-month depot formulation in subjects with CPP.

4.2 Study Design

This is a Phase 3, open-label, 2-part study in which the safety, efficacy, and pharmacokinetics/pharmacodynamics of a leuprolide acetate 45 mg 6-month (LA 45 mg 6-month) formulation will be evaluated in children with CPP. Part 1 (initial treatment) will be 52 weeks in duration, including at 4-week Screening Period and 48-week treatment period. Part 2 (a long-term extension of Part 1) will be 108 weeks in duration, including a 96-week treatment period and a 12-week follow-up period.

4.2.1 Study Design and Design Diagram

The total duration of the study (Parts 1 and 2) will be 160 weeks as follows:

- Part 1: 52 weeks (4-week screening period + 48-week treatment period)
- Part 2: 108 weeks (additional 96-week treatment period + 12-week follow-up period)

Part 1: The safety, efficacy, pharmacokinetics, and pharmacodynamics of the LA 45 mg 6-month dose will be evaluated in subjects with CPP from Baseline to Week 48. In all subjects, blood samples for efficacy assessments (analysis of LH, testosterone concentrations [males], and estradiol concentrations [females]) will be collected at Baseline and at Weeks 1, 4, 12, 20, 24, 44, and 48 after dosing. In the first subjects who are enrolled (20 subjects total, with at least 8 naïve and 8 previously treated), concentrations of leuprolide will be measured at each study visit following administration of LA 45 mg 6-month to characterize the leuprolide concentration-time profile, rate of absorption, and pharmacokinetic/pharmacodynamic relationship of leuprolide and LH. Investigative sites will be notified when the pharmacokinetic subset has been fulfilled.

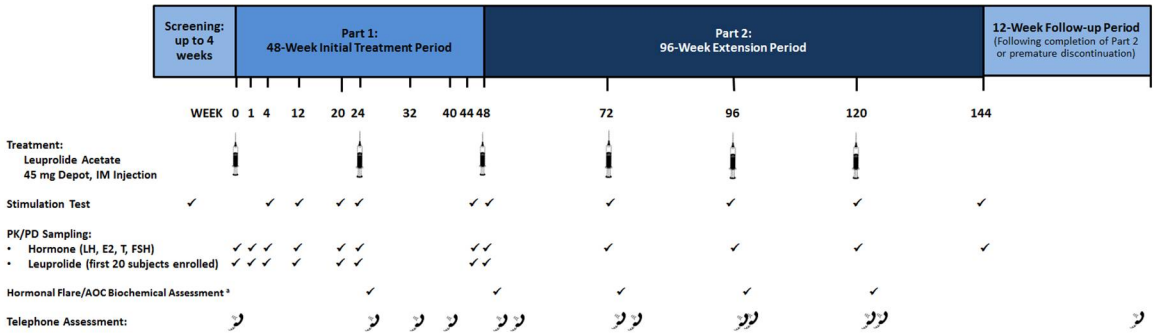
Leuprolide and appropriate measures of efficacy (LH, estradiol in females, testosterone in males) will be monitored upon data availability to evaluate the appropriateness of the 24-week dosing interval for the 6-month formulation for CPP.

Part 2: Following completion of Part 1 (the initial 48-week treatment period) assessments, subjects will continue to Part 2 of the study (extension period) to evaluate long-term administration of LA 45 mg 6-month (up to 24 months). Study visits during the extension period will start at Week 48 and continue once every 24 weeks for 96 weeks (24 months) until the subject discontinues treatment of LA 45 mg 6-month or withdraws from the study. Subjects will be assessed for continued maintenance of LH suppression and safety throughout this extension period.

A schematic of the study is shown in Figure 1.

Figure 1. Study Schematic

Children with CPP (N = ~40)



AOC = acute-on-chronic; E2 = estradiol; T = testosterone

a. At the beginning of Part 2, subjects will be randomly selected for AOC biochemical assessments 48 hours following the injection at Weeks 48, 72, 96, and 120.

Note: Week 0 = Day 1 (Baseline).

Note: See Operations Manual for details.

4.2.2 Variables Used for Stratification at Enrollment

All subjects in this study will receive the same treatment; therefore, no treatment randomization will be performed. A minimum of 15 of whom must be naïve to treatment with a GnRHa, and a minimum of 15 of whom must have been previously treated with a GnRHa.

At the beginning of Part 2, using the IRT system, half of the subjects will be randomly selected to have AOC biochemical assessment 48 hours after the injection at Weeks 48, 72, 96, and 120. Randomization will be stratified based on previous GnRHa treatment status (treatment-naïve or previous treated with a GnRHa). The randomization schedule will be generated and kept by the statistics department at AbbVie and a copy will be forwarded to the IRT provider.

4.3 Endpoint

Efficacy endpoints will be based on hormonal suppression. Stabilization or regression of signs of puberty, and effects on bone age and growth rate will be studied.

4.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with suppression of GnRHa-stimulated LH (< 4 mIU/mL) at Week 24 after the first dose of study drug but before the Week 24 dose. The null hypothesis is that less than 75% of subjects will achieve suppression of GnRHa-stimulated LH (< 4 mIU/mL) at Week 24.

4.3.2 Secondary Efficacy Endpoints

The following key secondary efficacy endpoints will be summarized:

- Proportion of subjects with suppression of GnRHa-stimulated LH (< 4 mIU/mL) at Weeks 12, 20, 24, 44, and 48.
- Proportion of female subjects with suppression of basal estradiol to < 20 pg/mL at Weeks 12, 20, 24, 44, and 48.
- Proportion of male subjects with suppression of testosterone to < 30 ng/dL at Weeks 12, 20, 24, 44, and 48.
- Proportion of subjects with maintenance of suppression of GnRHa-stimulated LH (< 4 mIU/mL) at Weeks 72, 96, 120, and 144.
- Proportion of female subjects with maintenance of suppression of basal estradiol to < 20 pg/mL at Weeks 72, 96, 120, and 144.
- Proportion of male subjects with maintenance of suppression of testosterone to < 30 ng/dL at Weeks 72, 96, 120, and 144.
- Proportion of subjects with suppression of the physical signs of puberty (breast development in females; testicular or genital development in males) at each scheduled assessment using modified Tanner staging.
- Incremental growth rate (cm/year) at each scheduled assessment.
- Ratio of change from Baseline in bone age to change from Baseline in chronological age at each scheduled assessment.

4.3.3 Other Efficacy Endpoints

The following other efficacy endpoints will be summarized:

- Peak stimulated LH concentrations at each scheduled assessment (not already specified in Section 4.3.2).
- Number and percentage of subjects who fail suppression of peak stimulated LH per primary endpoint analysis at each scheduled assessment.
- Number and percentage of female subjects with menstrual bleeding.
- Change from baseline in basal and peak stimulated LH, FSH, as well as basal and stimulated estradiol (for females) and testosterone (for males), to each scheduled assessment.
- Ratio and change from baseline in the ratio of bone age to chronological age at each scheduled assessment.
- Regression or no progression in pubic hair in both females and males.
- Change from baseline in uterine length, uterine volume, and ovarian volume to each scheduled assessment.
- Number and percentage of subjects with endometrial stripe presence by baseline endometrial stripe presence status (yes/no) at each scheduled assessment.
- Change from baseline in testicular length (cm), penile length (cm), and penile width (cm) by physical examination, and in testicular volume by Prader beads to each scheduled assessment.
- Change from baseline in BMI standardized score to each scheduled assessment
- Change from baseline in height standardized score to each scheduled assessment
- PedsQL and PROMIS questionnaires at each scheduled assessment.

4.3.4 Safety Endpoints

Safety evaluations are adverse events, physical examinations, vital sign measurements, LA 45 mg injection site reactions, hormonal flare and acute-on-chronic (AOC) response, and clinical laboratory testing as measures of safety and tolerability for the duration of the entire study.

4.4 Sample Size Justification

No formal sample size calculation was performed. Based on previous studies and historical precedent used for registration (n = ~40), 40 subjects are sufficient to support the safety and efficacy for this class of compounds in this patient population. The planned sample size of 40 subjects will provide an observed response rate (of suppression of peak stimulated LH) that is within 16.7% of the true response rate with 95% confidence.

4.5 Interim Analysis

No interim analysis will be performed.

4.6 End of Part 1 Analysis

At the end of Part 1, an analysis of the primary, secondary and other efficacy variables collected during part 1 of the study, along with demographic and safety variables, will be performed after the last subject completes the Week 48 assessment. These analyses will include data collected during Part 1 and should not include data collected during Part 2 or during the Follow-Up Period with the exception that Week 48 may include limited data after Week 48 dose if the data is considered as Week 48. The database will be versioned for an interim soft lock and any discrepant data will be clarified before the versioning. Analyses will be performed by AbbVie.

4.7 End of Part 2 Analysis

At the end of Part 2, an analysis of the appropriate efficacy and safety variables will be performed after the last subject completes the study. Analyses will be performed by AbbVie.

4.8 Multiplicity Testing Procedures for Type-I Error Control

There will be no adjustment for multiple endpoints as there is no hypothesis being tested.

4.9 Missing Data Imputation

Unless otherwise stated, data will be summarized as observed, i.e., missing data will not be imputed.

For the endpoint of suppression of GnRHa-stimulated LH, subjects who received study drug at the Day 1 visit and are missing GnRHa-stimulated LH results at a scheduled visit in Part 1 will be counted as LH suppression failures for that visit.

5.0 Analysis Populations and Important Subgroups

5.1 Analysis Population

The Full Analysis Set (FAS) consists of all subjects who received at least 1 dose of study drug. The FAS will be used for all efficacy and baseline analyses.

The safety Analysis Set consists of all subjects who received at least 1 dose of study drug.

5.2 Subgroup Analysis

Analysis of the primary efficacy endpoint will be conducted for the following subgroups by previous GnRHa treatment status and combined:

- Sex (males, females)
- Race (White, Black, or Other)
- Baseline LH value (< 4 miU/mL, ≥ 4 mIU/mL)
- Time between onset of puberty and start of treatment ((≤ Median, > Median)
- Age at onset of puberty (≤ Median, > Median)
- Predicted adult stature compared to lower bound of range of target height (<, ≥)
- Baseline BMI SD score (≤ Median, > Median)

6.0 Study Drug Duration

Duration (days) of treatment will be summarized for the Safety Analysis Set using the number of subjects treated, mean, standard deviation, median, minimum, and maximum.

Study drug duration will be summarized as follows:

Part 1 of the Treatment Period:

Last day of study drug for Part 1 – First dose date for Part 1 + 1

Part 2 of the Treatment Period:

Last day of study drug for Part 2 – First dose date for Part 2 + 1

In addition, the number and percentage of subjects will be summarized separately for Part 1 and Part 2 for the following categories:

- Number of injections that each subject received (1 or 2)
- Compliance or non-compliance with the dosing scheme. A subject will be considered non-compliant with the dosing scheme if there was a gap larger more than 3 days gap between the last day of one injection and the day of the next injection.

7.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

Demographics, baseline characteristics, medical history, prior medication, and concomitant medication will be summarized by previous GnRHa treatment status and overall using the Full Analysis Set. Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum, and maximum).

7.1 Demographics and Baseline Characteristics

Continuous demographic variables include age, weight, height, body mass index (BMI), and BMI SD score. Categorical demographic variables include sex, ethnicity, and race.

For CPP history, age at onset of CPP (in years), time between onset of puberty and start of CPP treatment (in years), time since first seen by a physician for CPP to start of CPP treatment (in years) will be summarized by sex and overall.

For family history, target height, mother's age at puberty and height, father's age at puberty and height will be summarized by sex and overall.

For bone age (in years) and height (in cm) related parameters, bone age, BA/CA (ratio of bone age to chronological age), BA-CA (bone age minus chronological age), and growth rate (cm/year) will be summarized by sex and overall.

For diagnostic results for CPP at baseline, brain tumor presence by MRI, brain tumor presence by CT scan, other brain abnormality by MRI, other brain abnormality by CT scan, and adrenal gland abnormality (yes) will be summarized by sex and overall.

In addition, the following baseline disease characteristics will be summarized for female and male:

- For female: tanner staging of breast, tanner staging of pubic hair, menarche status (yes/no), age at first menstruation (in years), bleeding per month (in days), spotting per month (in days), bleeding or spotting per month (in days), uterine length (in cm), uterine/ovary abnormality presence (yes), uterine volume, left ovarian volume, right ovarian volume, endometrial stripe presence (yes), thickness of endometrial stripe (in mm).
- For male: tanner staging of genitalia, tanner staging of pubic hair, left testicular volume, left testicular length, right testicular volume, right testicular length, and testicular abnormality presence (yes).

7.2 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. The number and percentage of subjects in each medical history category (by MedDRA system organ class and preferred term) will be summarized for the FAS. The system organ class (SOC) will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term).

7.3 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by generic drug name using the World Health Organization (WHO) Drug Dictionary.

Prior medications are those medications with a start date prior to the first study drug administration date. Prior medications will be summarized separately for prior CPP medications and other medications.

Concomitant medications during Part 1 are those medications, other than study drug, taken during the Part 1 of Treatment Period with an end date after the first dose of study drug or ongoing at the end of the study, and a start date prior to the last day of study drug for Part 1. Concomitant medications during Part 2 are those medications, other than study drug, taken during the Part 2 of Treatment Period with an end date after the first dose of study drug at Part 2 or ongoing at the end of the study, and a start date prior to the last day of study drug for Part 2.

8.0 Efficacy Analyses

8.1 General Considerations

For all efficacy endpoints, the descriptive statistics will be provided by previous GnRHa treatment status (naïve or previously treated) and combined. The descriptive statistics

include the number of observations, mean, standard deviation, minimum, median, and maximum for continuous variables; and number and percentage for categorical variables.

Subjects with missing GnRHa-stimulated LH test results at a specific scheduled visit will be counted as suppression failures for that visit.

8.2 Primary Efficacy Analysis

The primary efficacy endpoint is the proportion of subjects with suppression of GnRHa-stimulated LH (< 4 mIU/mL) at Week 24, after the first dose of study drug but before the Week 24 dose. The numerator will be the number of subjects with suppression of GnRHa stimulated LH (< 4 mIU/mL) at Week 24, and the denominator will be the number of subjects who received study drug at the Day 1 visit. The proportion of subjects suppressed and the two-sided 95% confidence interval based on the binomial distribution (Clopper-Pearson exact method) will be provided by previous GnRHa treatment status and overall. Peak stimulated LH will be calculated by taking the maximum LH concentrations observed at 30 or 60 min following a GnRHa stimulation test for scheduled assessments.

8.3 Secondary Efficacy Analyses

Unless otherwise specified, categorical data will be summarized by number and percentage; and continuous data will be summarized by sample size, mean, median, standard deviation, minimum, and maximum.

For the proportion of subjects with LH suppression at each scheduled assessment, the numerator will be the number of subjects with suppression of GnRHa stimulated LH (< 4 mIU/mL) at that visit, and the denominator will be the number of subjects who received study drug at the Day 1 visit. The proportion and the two-sided 95% confidence interval based on the binomial distribution (Clopper-Pearson exact method) will be provided by previous GnRHa treatment status and overall.

For the number and percentage of subjects with suppression of basal sex steroids, the two-sided 95% confidence intervals based on the binomial distribution (Clopper-Pearson exact method) will be provided by previous GnRHa treatment status and overall. For the percentage of subjects with suppression of basal sex steroids, if a subject did not received study drug at the prior scheduled injection visit, the subject will be excluded from the denominator. For example, if Week 24 injection is not done then any assessments after Week 24 the subject will be excluded from the denominator.

8.4 Other Efficacy Analyses

Unless otherwise specified, categorical data will be summarized by number and percentage; and continuous data will be summarized by sample size, mean, median, standard deviation, minimum, and maximum.

For the number and percentage of subjects who fail suppression of peak stimulated LH per primary endpoint analysis, the 95% confidence intervals will also be provided.

9.0 Safety Analyses

9.1 General Considerations

The Safety Analysis Set consists of all subjects who received at least 1 dose of study drug. All safety analyses will be performed by previous GnRHa status (naïve or previously treated), and overall.

The following summary statistics will be presented for subjects who have both baseline and post-baseline values for laboratory parameters and vital signs: the mean value at baseline and at each respective protocol specified visit, and the mean, standard deviation and median for changes from Baseline. Categorical data will be summarized using frequencies and percentages.

9.2 Analysis of Adverse Events

9.2.1 Treatment-Emergent Adverse Events

Treatment emergent adverse events are defined as any event with an onset date that is after the first dose of study drug and with an onset date no more than 12 weeks after the end of the effect of study drug (24 weeks after the date of the last administration of study drug). Events where the onset date is the same as the study drug start date are assumed to be treatment emergent.

9.2.1.1 Adverse Event Overview

The number and percentage of subjects experiencing treatment-emergent adverse events will be summarized for the following AE categories. In addition, the number and percentage of subjects experiencing treatment-emergent adverse events per 100 patient-years will be summarized.

- Any treatment-emergent adverse events
- Any treatment-emergent adverse events related to COVID-19
- Any treatment-emergent adverse events that was rated as related to study drug by the investigator
- Any treatment-emergent severe adverse events
- Any treatment-emergent serious adverse events
- Any treatment-emergent adverse events leading to discontinuation of study drug
- Any treatment-emergent adverse events leading to death
  - Deaths occurring ≤ 36 weeks after last dose of study drug
  - Deaths occurring > 36 weeks after last dose of study drug
- Any treatment-emergent adverse event of special interest

9.2.1.2 Adverse Events by System Organ Class and Preferred Term

The number and percentage of subjects experiencing treatment-emergent adverse events will be tabulated using primary Medical Dictionary for Regulatory Activities (MedDRA) by System Organ Class (SOC) and Preferred Term (PT). Subjects reporting more than one adverse event for a given PT will be counted only once for that term (most severe incident for the severity tables and most related incident for the relationship tables). Subjects reporting more than one type of adverse event within a SOC will be counted only once for that SOC. Subjects reporting more than one type of adverse event will be counted only once in the overall total.

9.2.1.3 Adverse Events by Preferred Term

The number and percentage of subjects experiencing treatment-emergent adverse events will be tabulated by Preferred Term (PT) by decreasing frequency of overall.

9.2.1.4 Adverse Events by Maximum Relationship

Treatment emergent adverse events will be summarized by maximum relationship to study, as assessed by the investigator. If a subject has an adverse event with unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship present. The only exception is if the subject has another occurrence of the same adverse event with a relationship assessment of "Reasonable Possibility." In this case, the subject will be counted under the "Reasonable Possibility" category.

9.2.1.5 Adverse Events by Maximum Severity

Treatment-emergent adverse events will be summarized by maximum severity. If a subject has an adverse event with unknown severity, then the subject will be counted in the severity category of "unknown," even if the subject has another occurrence of the same event with a severity present. The only exception is if the subject has another occurrence of the same adverse event with the most extreme severity – "Severe." In this case, the subject will be counted under the "Severe" category.

9.2.1.6 Adverse Events of Special Interest

Adverse events of special interest will be summarized by SOC and PT and will be based on standardized or company MedDRA queries (SMQs or CMQs), or based on adjudication results.

The following Adverse Events of Special Interest (AESI) will be summarized:

- Bone fracture
- Slipped capital femoral epiphysis
- Neuropsychiatric events
- Seizure/convulsion
- Injection site reaction
- Hypersensitivity reactions

Detailed information about the search criteria is provided in Appendix A.

9.2.1.7 Hormonal Flare Response Adverse Events

The number and percentage of subjects with hormonal flare response adverse events will be by summarized by SOC and PT.

Data on acute-on-chronic symptoms collected from phone calls and visits after study drug injections will be summarized with number and percentage for who reported abnormal behavior, abnormal physical symptoms or any abnormalities.

A blood sample will be collected 48 hours after the second injection (Week 24) of LA 45 mg 6-month, which will be used to assess the biochemical AOC phenomenon by measuring LH and estradiol (female subjects) or testosterone (male subjects) in all subjects (both pre-treated and naïve). The AOC biochemical definition is LH > 4 mIU/mL and estradiol > 20 pg/mL or testosterone > 30 ng/dL 48 hours after the second injection of leuprolide acetate at the Week 24 visit. The number and percentage of subjects with biochemical AOC phenomenon will be provided.

9.3 Analysis of Laboratory Data

Data collected from central and local laboratories, including additional laboratory testing due to an SAE, will be used in all analyses, except for Baseline where SAE-related laboratory assessments on or before the first dose of study drug will be excluded. The clinical laboratory tests defined in the protocol operations manual (i.e., hematology and clinical chemistry) will be summarized.

Each laboratory variable will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from baseline to each applicable post-baseline visit will be summarized for selected laboratory variables, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error, and 95% confidence interval will be presented for the mean change from baseline.

Below are selected laboratory variables:

Hematology	Platelet count, hemoglobin, white blood cell (WBC) count, Lymphocytes, Neutrophils
Chemistry	Albumin, Alkaline Phosphatase, ALT, AST, Bilirubin, Creatinine, Glucose, Potassium, Magnesium, Sodium

Changes in selected laboratory parameters will be tabulated using shift tables by NCI CTC criteria and categorized as low, normal, or high based on the normal ranges of the laboratory used for each sample. A shift table from baseline either to the worse value (based on NCI CTC criteria) during treatment or to minimum and maximum value (based on normal range), will be created. A similar shift table will be provided to summarize shifts from baseline to the final post-baseline value.

In addition, the number and percentage of subjects who have potentially clinically significant (PCS) laboratory values meeting the following criteria any time during the appropriate Treatment Period will be summarized. Listings will be provided to summarize subject-level laboratory data for subjects meeting PCS criteria.

Analyte	PCS Low Threshold	PCS High Threshold
Hematocrit	≤ 24%	≥ 54%
Hemoglobin	≤ 8.0 g/dL	≥ 16 g/dL
Red Cell Count	≤ 2.5×10^6/uL	≥ 7.0×10^6/uL
MCV	≤ 0.8 × LLN	≥ 1.2 × ULN
MCH	≤ 0.8 × LLN	≥ 1.2 × ULN
MCHC	≤ 0.8 × LLN	≥ 1.2 × ULN
White Cell Count	≤ 3×10^3/uL	≥ 16×10^3/uL
Platelet Count	≤ 100×10^3/uL	≥ 800×10^3/uL
Neutrophils Absolute	≤ 1.0×10^3/uL	≥ 12.0×10^3/uL
Lymphocytes Absolute	2y – 4y: ≤ 1.0×10^3/uL > 4y: ≤ 0.5×10^3/uL	> 2y-4y: ≥ 15×10^3/uL > 4y: ≥ 10×10^3/uL
Monocytes Absolute	≤ 0.1×10^3/uL	≥ 3.0×10^3/uL
Eosinophils Absolute		≥ 1.0×10^3/uL
Basophils Absolute		≥ 0.6×10^3/uL
Albumin	≤ 2.0 g/dL	≥ 6.0 g/dL
Alkaline Phosphatase		≥ 2 × ULN
ALT		≥ 2 × ULN
AST		≥ 2 × ULN
Bilirubin		≥ 2 × ULN
Lactate Dehydrogenase		≥ 2 × ULN
Creatinine	≤ 0.3 mg/dL	≥ 1.5 mg/dL or increase by 0.3 mg/dL
Magnesium	≤ 1.0 mg/dL	≥ 3.5 mg/dL
Glucose	≤ 50 mg/dL	≥ 180 mg/dL
Chloride	≤ 90 mEq/L	≥ 115 mEq/L
Bicarbonate	≤ 16 mEq/L	≥ 35 mEq/L
Calcium	≤ 7.0 mg/dL	≥ 13.0 mg/dL
Potassium	≤ 3.0 mEq/L	≥ 6.0 mEq/L
Sodium	≤ 130 mEq/L	≥ 155 mEq/L

9.4 Analysis of Vital Signs and Weight

For blood pressure, respiratory rate, temperature, weight, BMI, and BMI SD score, the sample size, mean, standard deviation, median, minimum, and maximum will be

summarized. In addition, mean changes from baseline to each scheduled assessment will be summarized with the baseline mean, visit mean, change from baseline mean, standard deviation, and median.

10.0 Summary of Changes

10.1 Summary of Changes Between the Previous Version and the Current Version

Remove the laboratory values in Section 9.3 that are not supported by CTCAE criteria 4.03.

10.2 Summary of Changes in Previous Version

Summary of changes between the second version and the third version include:

- Section 4.9 Missing Data Imputation has been updated for the endpoint of suppression of GnRHa-stimulated LH. Subjects who received study drug at Day 1 visit and are missing results in Part 1 will be considered as LH suppression failures.
- Addition of Subgroup Analysis in Section 5.2
- Addition of Study Drug Duration in Section 6.0
- Addition of Section 7.0 for analyses for demographics, baseline characteristics, medical history, and prior/concomitant medications
- Section 9.2.1.1 Adverse Event Overview has been updated to include AE related to COVID-19 and deaths occurring ≤ or > 36 weeks after last dose of study drug
- Section 9.2.1.4 Adverse Events by Maximum Relationship has been updated to change "Possibly or Definitely related" to "Reasonable Possibility" to align with eCRF.
- Section 9.2.1.7 Hormonal Flare Response Adverse Events has been updated to add a description of analysis for hormonal flare response adverse event and to update the definition of biochemical AOC phenomenon
- Section 9.3 Analysis of Laboratory Data has been updated with more details
- Addition of Appendix A for definition of AESI

Summary of changes between the initial and second version includes the following:

The primary, secondary and other efficacy endpoints have been updated to reflect changes in protocol. The primary efficacy endpoint has been changed to the proportion of subjects with suppression of GnRHa-stimulated LH (< 4 mIU/mL) at Week 24 after the first dose of study drug. The secondary and other efficacy endpoints have been updated in Section 4.3.2 and Section 4.3.3. The analysis for the primary efficacy endpoint has been changed to two-sided 95% confidence interval based on the binomial distribution (Clopper-Pearson exact method).

Appendix A. Definition of Adverse Events of Special Interest (AESI)

Adverse Events of Special Interest (AESI) will be identified using the following search criteria:

Item of Safety Interest	Method of Surveillance
Bone fracture	Bone fractures CMQ
Slipped capital femoral epiphysis	Fractures HLGT and Epiphyseal disorders HLT (limit to under 18 years of age)
Neuropsychiatric events	Suicide/self-injury SMQ_Narrow
Seizure/convulsion	Convulsions SMQ_Broad
Injection site reaction	Injection site reaction CMQ
Hypersensitivity reactions	Hypersensitivity SMQ Narrow