



Protocol for Study M16-904

Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of Leuprolide Acetate 45 mg 6-month formulation in Children with Central Precocious Puberty

VERSION: 3.0 DATE: 05 August 2020

SPONSOR: AbbVie Inc.* NUMBER OF SITES: Approximately 20 (United States and Puerto Rico)

ABBVIE INVESTIGATIONAL PRODUCT: Leuprolide acetate

FULL TITLE: A Phase 3, Multicenter, 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 (CPP)

Incorporating Versions 1, 2, and 3 and Administrative Change 1

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1 SYNOPSIS

Title: A Phase 3, Multicenter, 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 (CPP)	
Background and Rationale:	Treatment of central precocious puberty (CPP), a pediatric orphan disease, can require frequent injections (e.g., once every 1 to 3 months) of a gonadotropin-releasing hormone agonist (GnRHa) for up to 10 years to arrest premature development of secondary sexual characteristics. Development of a longer-acting depot formulation would reduce the number of injections.
Objectives and Endpoints:	<p>Objectives</p> <ul style="list-style-type: none"> • The primary objective of the study is to assess the safety and efficacy of a leuprolide acetate (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. • The secondary objective is 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. <p>Endpoints</p> <ul style="list-style-type: none"> • The primary efficacy endpoint is the proportion of subjects with suppression of GnRHa-stimulated luteinizing hormone (LH) (< 4 mIU/mL) at Week 24 after the first dose of study drug but before the Week 24 dose. • The secondary efficacy endpoints are: <ul style="list-style-type: none"> • Proportion of subjects with suppression of GnRHa-stimulated LH (< 4 mIU/mL) at Weeks 12, 20, 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.

	<ul style="list-style-type: none"> • Proportion of subjects with suppression of the physical signs of puberty (breast development in females; testicular volume 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/change from Baseline in chronological age at each scheduled assessment. • Other efficacy endpoints: <ul style="list-style-type: none"> • Peak stimulated LH concentrations at each scheduled assessment. • 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 and 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. • Safety evaluations are adverse event monitoring, physical examinations, vital sign measurements, LA 45 mg injection site reactions, hormonal flare and acute-on-chronic (AOC) response, and clinical laboratory testing.
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	<ul style="list-style-type: none"> • Pharmacokinetic/pharmacodynamic endpoints are to characterize the pharmacokinetics of LA 45 mg 6-month dose in children with CPP as well as describe the relationship between leuprolide concentration and pharmacodynamics (stimulated LH) over 48 weeks.
Investigators:	Multicenter
Study Sites:	Approximately 20 (United States and Puerto Rico)
Study Population and Number of Subjects to be Enrolled:	Approximately 40 male and female children with CPP, 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.
Investigational Plan:	This is a Phase 3, open-label, 2-part study in which the safety, efficacy, and pharmacokinetics/pharmacodynamics of an LA 45 mg 6-month formulation will be evaluated in children with CPP. Part 1 (initial treatment) will be 52 weeks in duration and will consist of a 4-week Screening Period and 48-week treatment period. Part 2 (a long-term extension of Part 1) will be 108 weeks in duration and will consist of a 96-week treatment period and a 12-week follow-up period.
Key Eligibility Criteria:	Children with CPP who are naïve to treatment with a GnRHa (females 2 – 8 years of age, inclusive, or males 2 – 9 years of age, inclusive) or who have been on standard GnRHa therapy for at least 6 months (females 2 – 10 years of age, inclusive, or males 2 – 11 years of age, inclusive).
Study Drug and Duration of Treatment:	LA 45 mg 6-month depot formulation administered every 24 weeks for up to 48 weeks in Part 1 and up to 96 additional weeks in Part 2.
Date of Protocol Synopsis:	05 August 2020

2 INTRODUCTION

2.1 Background and Rationale

Why This Study is Being Conducted

Central precocious puberty (CPP) is an orphan disease that affects the pediatric population. Gonadotropin-releasing hormone agonists (GnRHa) are the treatment of choice for CPP. The goal of therapy is to suppress pituitary gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) and peripheral sex steroids (estradiol and testosterone) and to arrest premature progression of secondary sexual characteristics. Children with CPP may require extended therapy (up to 10 years) to achieve continuous hormonal suppression until they reach an age at which the patient, family, and practitioner agree that puberty should resume.

Leuprolide acetate (LA) is a GnRHa that is approved in the United States (US) and other countries for the treatment of children with CPP. It is marketed as Lupron Depot-PED® in the US. Lupron Depot is also approved in the US and other countries for the treatment of prostate cancer, endometriosis, and uterine leiomyomata. Lupron Depot-PED is available in 1-month formulations (7.5, 11.25, and 15 mg) and 3-month formulations (11.25 and 30 mg) for the treatment of children with CPP in the US.

The Lupron Depot 45 mg 6-month dose is approved for the treatment of adults with prostate cancer; this is the same formulation that is being investigated for use for treatment of CPP and contains the same active ingredient as the 1- and 3-month formulations of Lupron Depot-PED in a prefilled dual chamber syringe.

The currently approved Lupron Depot-PED regimens for CPP require 4 to 12 injections per year. The need for frequent injections can cause distress for both the child and the parents (or legal guardians) and may require absences from school for the child and absences from work for parents (or legal guardians). While longer-acting GnRHa treatments (implants) are available, these treatments require general anesthesia to surgically place and remove. Development of a longer-acting depot formulation for children with CPP would reduce the number of injections and provide more treatment options for health care providers; a longer-acting formulation may also reduce the number of occurrences of injection site pain, which is the most commonly reported adverse event related to treatment of children with CPP with Lupron Depot-PED (see Section 2.2). LA 45 mg 6-month has not been studied in children with CPP.

2.2 Benefits and Risks to Subjects

The benefits of treatment with LA for children with CPP are well documented: improvements in the signs and symptoms of CPP, suppression of pubertal gonadotropin and/or sex steroid levels, halting the progression and/or promoting the regression of Tanner stages, and slowing or halting of epiphyseal closures that may lead to an increase in final adult height.¹

The overall safety of Lupron Depot-PED 11.25 mg 3-month and 30 mg 3-month is well characterized, with approximately [REDACTED] doses having been administered to pediatric patients worldwide, representing approximately [REDACTED] patient-years of exposure. In addition, Lupron Depot-PED 11.25 mg

3-month and 30 mg 3-month were evaluated in a study in children with CPP (Study L-CP07-167)² and in a 36-month extension study (Study L-CP07-177).³ The safety profile of LA 45 mg 6-month in children with CPP is expected to be similar to that of the approved Lupron Depot-PED formulations for the treatment of CPP with similar hormonal changes (initial flare effect with corresponding LH/estradiol/testosterone elevations followed by a rapid decline to prepubertal levels).

Since LA 45 mg 6-month is administered as an intramuscular injection, injection site pain following dosing is a potential safety risk. Injection site pain following Lupron Depot dosing was the most commonly reported adverse event in children with CPP in Study L-CP07-167 (Lupron Depot-PED 11.25 and 30 mg 3-month formulations); injection site pain was also a commonly reported adverse event in adults with prostate cancer in a 6-month study of the 45 mg formulation (Study L-PC07-169). Injection site pain occurred in 26% of pediatric subjects in the 30 mg group and 19% of pediatric subjects in the 11.25 mg group in Study L-CP07-167. Injection site pain occurred in 18% of adult subjects with prostate cancer in the 45 mg 6-month study (Study L-PC07-169).

All adverse events of injection site pain in pediatric subjects were mild to moderate in intensity in the 11.25 mg 3-month and 30 mg 3-month groups in Study L-CP07-167, with the exception of a severe adverse event of injection site pain in 1 subject in the 30 mg group. Similarly, in Study L-CP07-177 (an extension of Study L-CP07-167), only 1 severe event of injection site pain was reported (1 subject in the 11.25 mg group). No increase in incidence over time or worsening in intensity was apparent.

See the current package inserts for a more comprehensive listing of known and potential safety risks and benefits.

3 OBJECTIVES AND ENDPOINTS

Objectives and Hypotheses

Primary

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.

The hypotheses corresponding to the primary objective are that treatment of children with CPP with LA 45 mg 6-month is well tolerated and effectively maintains continuous hormonal suppression following administration. Administration of 1 intramuscular dose of LA 45 mg 6-month provides sufficient leuprolide serum concentrations to achieve suppression of LH (determined by peak stimulated LH < 4 mIU/mL) at Week 24 in children with CPP.

Secondary

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.

3.1 Primary 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.

3.2 Secondary Endpoints

Secondary endpoints:

- Proportion of subjects with suppression of GnRHa-stimulated LH (< 4 mIU/mL) at Weeks 12, 20, 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 volume or genital development in males) at each scheduled assessment using modified Tanner staging.^{4,5}
- Incremental growth rate (cm/year) at each scheduled assessment.
- Ratio of change from Baseline in bone age/change from Baseline in chronological age at each scheduled assessment.

3.3 Other Efficacy Endpoints

Other efficacy endpoints:

- Peak stimulated LH concentrations at each scheduled assessment.
- 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 and 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 body mass index (BMI) standardized score to each scheduled assessment.
- Change from Baseline in height standardized score to each scheduled assessment.
- Pediatric Quality of Life Inventory (PedsQL) and Patient Reported Outcomes Measurement Information System (PROMIS) questionnaires at each scheduled assessment.

3.4 Safety Endpoints

Adverse events, physical examinations, vital sign measurements, LA 45 mg injection site reactions, hormonal flare and acute-on-chronic (AOC) response, and clinical laboratory test results will be assessed throughout the study.

3.5 Pharmacokinetic/Pharmacodynamic Endpoints

The pharmacokinetics of leuprolide will be evaluated using population pharmacokinetic analysis. Furthermore, the relationship between leuprolide pharmacokinetics and clinical response (pharmacodynamics of leuprolide measured as LH, testosterone [males], and estradiol [females]) in children with CPP will be examined.

The objectives of this population pharmacokinetic/pharmacodynamic analysis are as follows:

- To estimate the mean pharmacokinetic and pharmacodynamic (LH, testosterone [males], and estradiol [females]) parameters in a population of pediatric subjects with CPP.
- To investigate and identify fixed effect sources of variability (covariates) that may influence the pharmacokinetics/pharmacodynamics of leuprolide.
- To estimate the magnitude of inter-individual variability of the parameters.
- To measure the random residual variability.

Serum leuprolide and gonadotropin/sex hormone concentrations will be modeled using an appropriate pharmacokinetic/pharmacodynamic model to describe factors that influence leuprolide pharmacokinetic and pharmacodynamic response in children with CPP.

Other parameters, including parameters that describe leuprolide absorption characteristics, may be estimated if useful in the analysis.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

Study M16-904 is a Phase 3, open-label, multicenter study that will be conducted in 2 parts (Parts 1 and 2) at approximately 20 sites (US and Puerto Rico). The safety, efficacy, pharmacokinetics, and pharmacodynamics of the LA 45 mg formulation administered with a 6-month dosing interval in children with CPP will be evaluated. Approximately 40 subjects who were previously treated with GnRHa therapy (minimum of 15 previously treated subjects) or who are naïve to previous GnRHa treatment (minimum of 15 naïve subjects) will be enrolled in the study. See Section 5 for information regarding eligibility criteria.

LH and sex steroid suppression and pubertal symptom progression will be assessed. Efficacy endpoints are based on hormonal suppression. Stabilization or regression of signs of puberty and effects on bone age and growth rate will be evaluated.

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)

The Screening Period may be extended in certain circumstances (e.g., pending laboratory test results) following consultation with the sponsor.

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, FSH, 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, FSH, 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 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.

Note: Week 48 is the end of Part 1 and also the start of Part 2. See [Appendix D](#) of the protocol and Section 2 of the Operations Manual for details.

Some of the study visits and visit activities (including but not limited to clinical laboratory tests and concomitant medication assessment) may be conducted in a non-hospital/clinic environment (e.g., the subject's home) by qualified individuals at the request of the Investigator and with the agreement of AbbVie, the subject, and subject's parent or legal guardian.

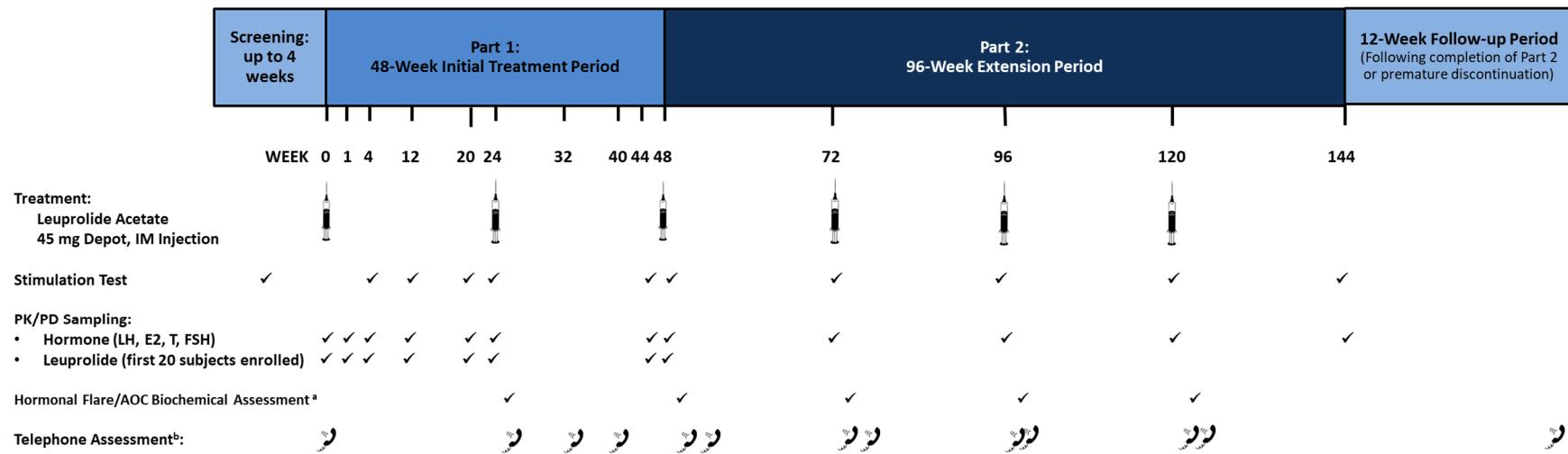
If a subject cannot come to the site because of an unforeseen circumstance (e.g., the COVID-19 pandemic), study visits may be conducted virtually by site staff (e.g., by phone or video) or by a qualified home healthcare nurse in a non-hospital/clinic environment (e.g., the subject's home) at the request of the investigator and with the agreement of the subject's parent or legal guardian. AbbVie should be notified if this occurs.

Details of the study procedures are located in the Operations Manual ([Appendix F](#)).

A schematic of the study is shown in [Figure 1](#).

Figure 1. Study Schematic

Children with CPP (N = ~40)



AOC = acute-on-chronic; CPP = central precocious puberty; E2 = estradiol; T = testosterone; FSH = follicle-stimulating hormone; IM = intramuscular; LH = luteinizing hormone; PK/PD = pharmacokinetic/pharmacodynamic

- At the beginning of Part 2, half of the subjects will be randomly selected for AOC biochemical assessments 48 hours after the injection of study drug at Weeks 48, 72, 96, and 120.
- For subjects randomly selected for AOC biochemical assessments 48 hours after the injection of study drug at Weeks 48, 72, 96, and 120, a single telephone assessment will take place 7 days following the injection of study drug. For subjects not selected for the AOC biochemical assessments, a telephone assessment will take place 1 day and 7 days following the injection of study drug at Weeks 48, 72, 96, and 120.

Notes: The Screening Period may be extended in certain circumstances (e.g., pending laboratory test results) following consultation with the sponsor. Week 0 = Day 1 (Baseline). See Operations Manual ([Appendix F](#)) for details of the study schematic.

Rescreening

Subjects who initially fail screening may be permitted to rescreen following re-consent. Sites must contact the AbbVie Therapeutic Area Medical Director (TA MD) to confirm whether subjects should or should not be rescreened. The subject must meet all eligibility criteria at the time of rescreening to qualify for the study. There is no minimum period of time a subject must wait to rescreen.

Laboratory assessments will not need to be repeated for subjects in rescreening if the time between screening and rescreening is less than 28 days; however, laboratory assessments will need to be repeated at Baseline if the time between laboratory assessments during previous Screening and Baseline is greater than 28 days.

4.2 Discussion of Study Design

Choice of Control Group

For ethical reasons, this study does not have a placebo control group, as intervention in this patient population is essential, and treatment should start immediately to maximize possible benefits of GnRHa treatment. Also, for ethical reasons, this study does not have an active control group, as differences in dosing frequencies would require sham injections.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be used in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with CPP. All clinical and laboratory procedures in this study are standard and generally accepted.⁶

Suitability of Subject Population

Both treatment-naïve subjects and those who were previously treated with a GnRHa were selected for this study, as both populations may benefit from the proposed extended dosing interval either as initial therapy or maintenance therapy, respectively.

Selection of Doses in the Study

The LA 45 mg 6-month dose in this study was chosen to extend the dosing interval to reduce the number of injections. The formulation chosen for this study is the same as the approved Lupron Depot 45 mg 6-month dose for prostate cancer and contains 45 mg of LA in a prefilled dual chamber syringe. LA is the same active ingredient as in the approved Lupron Depot-PED 11.25 mg 3-month and 30 mg 3-month CPP formulations. The injection volume for the 45 mg 6-month dose is also the same as that in the approved 11.25 mg 3-month and 30 mg 3-month CPP formulations. The same prefilled, dual chamber syringes and needles are used for the 3-month and 6-month formulations.

The average monthly dose of LA with a 45 mg 6-month dose is expected to be 7.5 mg because of the sustained release characteristics of the 45-mg formulation. This is consistent with that of the lower dose, shorter-duration formulations. This monthly exposure to leuprolide is identical to the lowest Lupron Depot-PED dose that is approved in the US (7.5 mg 1-month formulation) and is half that of the highest approved Lupron Depot-PED dose (15 mg 1-month formulation).

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria to be included in the study. Anything other than a positive response to the questions below will result in exclusion from the study.

Consent

- 1. Parent or legal guardian has voluntarily signed and dated an informed consent form, approved by an institutional review board (IRB), after the nature of the study has been explained and the subject and the subject's parent or legal guardian has had the opportunity to ask questions. The informed consent must be signed before any study-specific procedures are performed or before any concomitant medication is discontinued for the purpose of the study. Pediatric subjects will be included in all discussions in order to obtain verbal and/or written assent.

Disease Activity

- 2. Children with a diagnosis of CPP, either treatment-naïve or previously treated with a GnRHa.
- 3. Chronological age at the appearance of pubertal changes < 8 years in females and < 9 years in males at Day 1 of the study.

Demographic and Laboratory Assessments

- 4. Bone age advancement over chronological age at least 1 year at time of CPP diagnosis or first GnRHa therapy.
- 5. Bone age < 13 years for females and < 14 years for males.
- 6. In general good health with no uncontrolled, clinically significant disease that could interfere with bone maturation or mask the objectives of this protocol as assessed by the investigator.
- 7. No abnormal laboratory value that suggests a clinically significant underlying disease or condition that may prevent the subject from entering the study.
- 8. Willing and able to comply with procedures required in this protocol.
- 9. No diagnosis of short stature, i.e., more than 2.25 SD below the mean height for age (growth chart assessment).

Subject History

- 10. No diagnosis of incomplete precocious puberty, peripheral precocious puberty; evidence of any abnormal pituitary, hypothalamic, adrenal, thyroid, and gonadal function other than premature secretion of gonadotropins not adequately controlled; no unstable intracranial tumors (unresponsive to treatment/expanding) except hamartoma.

- 11. No concomitant medical condition that, in the opinion of the investigator, may expose a subject to an unacceptable level of safety risk or that affects subject compliance.
- 12. No history of clinically significant medical conditions or any other reason that the investigator determines would **interfere with the subject's participation** in this study or would make the subject an unsuitable candidate to receive study drug.
- 13. No history of an **allergic reaction** or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.

Pregnancy

- 14. A **negative serum pregnancy test** for female subjects \geq 10 years of age at Screening and negative urine pregnancy test on Day 1 prior to study drug administration. For female subjects $<$ 10 years of age, pregnancy tests may be performed at Screening and on Day 1 at the discretion of the principal investigator.

Concomitant Medications

- 15. Must have discontinued therapy with medroxyprogesterone acetate, growth hormone, insulin-like growth factor-1 (IGF-1), or estrogen or testosterone preparations at least 5 half-lives or 4 weeks prior to Screening, whichever is longer.
- 16. Must not have been treated with **any investigational drug** within 30 days or 5 half-lives of the drug (whichever is longer) prior to Screening or is currently enrolled in another clinical study.

Additional Criteria for Subjects Naïve to GnRHa treatment

- 17. Females 2 – 8 years of age, inclusive, or males 2 – 9 years, inclusive, on Day 1.
- 18. Pretreatment pubertal response to GnRHa stimulation test ($LH \geq 6$ mIU/mL) at Screening.
- 19. Breast pubertal staging (modified Tanner) of at least 2 in females; testicular volume of at least 4 cc in males at Screening.

Additional Criteria for Subjects Previously Treated with a GnRHa

- 20. Females 2 – 10 years of age, inclusive, or males 2 – 11 years of age, inclusive, on Day 1.
- 21. Must have been on GnRHa therapy for at least 6 months prior to Day 1.
- 22. Should have documented maintenance of LH suppression as evidenced by peak stimulated $LH < 4$ mIU/mL at Screening.

5.2 Prohibited Medications and Therapy

All other investigational drugs are prohibited during the study.

Any medications with a known positive or negative effect on either growth or the assessment of sex steroids will not be permitted for use during the study. Examples are as follows:

- GnRH agonists other than study drug*
- GnRH antagonists
- High dose corticosteroids (e.g., doses greater than hydrocortisone 5 mg/m² body surface area/day)
- Growth hormone
- IGF-1
- Testosterone
- Estrogen

*The GnRH agonist required to perform the stimulation test is allowed during the study (see Operations Manual Section 3.15).

5.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving within 30 days prior to Screening, at the time of enrollment, and during the study must be recorded through the 12-week follow-up phone call.

All medications used to treat the subject's CPP in the last 12 months prior to Screening, including all GnRHa medications, will be recorded in the appropriate electronic case report form (eCRF).

Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact (TA MD). Information regarding potential drug interactions with LA is located in the Lupron Depot package insert.

5.4 Withdrawal of Subjects and Discontinuation of Study

Study subjects and/or their parent or legal guardian have the right to prematurely withdraw from the study at any time.

The investigator may discontinue any subject's participation for any reason, including an adverse event, safety concerns, or failure to comply with the protocol.

Subjects will be withdrawn from the study immediately if any one of the following occurs:

- Clinically significant abnormal laboratory results or adverse events, which rule out continuation of study drug, as determined by the Investigator or the AbbVie TA MD.
- The subject requests withdrawal from the study.
- It is in the subject's best medical interest.

- Eligibility criteria violation was noted after the subject started study drug and continuation of study drug would place the subject at risk.
- Introduction of prohibited medications or dosages and continuation of study drug would place the subject at risk.
- An adverse event occurs that the investigator feels is detrimental to the subject.
- The subject requires treatment with another drug that will interfere with evaluation of the investigational product.
- Subject is significantly noncompliant with study procedures, which would put the subject at risk for continued participation in the trial.
- Subject demonstrates severe allergic reaction to the investigational product.
- Subject is pregnant.
- Subject is not adequately suppressed on therapy as evidenced by peak stimulated LH level of ≥ 4 mIU/mL at or after Week 24 **and** subject has an accelerated progression of pubertal symptoms any time after Week 24, specifically > 1 -stage progression in breast or genitalia (not pubic hair) from the last visit as assessed by the same individual, if possible.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 phone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

5.5 Follow-Up for Subject Discontinuation of Study Drug or from Study

To minimize missing data, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits, unless subjects and their parent or legal guardian have decided to discontinue study participation entirely (withdrawal of informed consent). Subjects and their parent or legal guardian should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit should be completed as soon as possible, preferably within 2 weeks. In addition, if the subject and parent or legal guardian is willing, a 12-week follow-up phone call after the last visit may be completed to ensure all treatment-emergent adverse events/serious adverse event (SAE) have been resolved.

5.6 Study Drug

LA 45 mg 6-month drug product, manufactured by Takeda Pharmaceuticals for AbbVie, will be injected intramuscularly beginning on Day 1, and will be administered by study site staff under the supervision of

the principal investigator or designee. In unforeseen circumstances (e.g., the COVID-19 pandemic), the study drug injection may be administered by a home healthcare nurse at the subject's home. Details are provided in Operations Manual Section 3.19.

LA 45 mg 6-month drug product will be provided by AbbVie in quantities sufficient to accommodate the study design. Each kit will be labeled per local requirements, and this label must remain affixed to the kit. Upon receipt, study drug should be stored at controlled room temperature (15° to 25°C/59° to 77°F) and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be administered at the subject's corresponding study visit. The site staff will complete the blank space on the label with the subject number before administering the study drug. Study drug will only be used for the conduct of this study.

AbbVie will provide instructions for drug preparation (refer to Section 7.3 of the Operations Manual).

AbbVie, the sponsor of this study, will source the generic LA aqueous solution for the GnRHa stimulation test and provide it to participating sites. The generic LA aqueous solution will either be from a US-registered source or an ex-US registered source (an investigative product comparable with the US-registered material). If a label is mandated by local agencies, a label may be applied. There may be times when the sponsor is unable to provide the generic LA aqueous solution. Under these circumstances, participating sites have the option to obtain this product through an external licensed pharmacy or wholesaler or from local site supplies. In unforeseen circumstances (e.g., the COVID-19 pandemic), the GnRHa stimulation test may be performed by a home healthcare nurse at the subject's home. Details are provided in the Operations Manual Section 3.15.

5.7 Randomization/Drug Assignment

All subjects in this study will receive the same treatment; therefore, subjects will not be randomized.

All subjects will be assigned a unique identification number by the IRT at the screening visit. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used. Enrollment will be limited by previous treatment status to ensure that a minimum of 15 subjects are treatment naïve and that a minimum of 15 subjects are previously treated with a GnRHa.

At Baseline, the IRT will assign 20 subjects to the pharmacokinetic subset. The first subjects enrolled in the study will automatically be assigned to the pharmacokinetic subset for collection of blood samples for the quantification of leuprolide concentration, with a minimum of 8 subjects naïve to GnRHa treatment (maximum of 12 subjects) and a minimum of 8 subjects who have been previously treated with a GnRHa (maximum of 12 subjects).

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 of study drug 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.

5.8 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified), the investigator is responsible for notifying the independent review board (IRB), regulatory authorities (as applicable), and AbbVie.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

An adverse event is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event, therefore, can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be adverse events.

Investigators will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. All adverse events will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure was pre-planned prior study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

If an adverse event, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance or contract research organization (as appropriate) as an SAE within 24 hours after the site becomes aware of the SAE (refer to Section 4.2 of the Operations Manual for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

**Important Medical Event
Requiring Medical or Surgical
Intervention to Prevent
Serious Outcome**

An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All adverse events reported from the time of study drug administration until 12 weeks after the end of the effect of study drug (24 weeks after the date of the last administration of study drug) will be collected, whether solicited or spontaneously reported by the subject. In addition, all SAEs and study procedure-related nonserious adverse events will be collected from the time the subject's parent or legal guardian signs the study-specific informed consent until study drug administration.

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product in accordance with global and local regulations.

Adverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Events of Special Interest

The following adverse events of special interest must be captured:

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

*All injection site reactions, whether associated with study drug administration or with the stimulation test, must be captured as adverse events. Any injection site reaction that reaches seriousness criteria as stated above will be captured as an SAE and reported as described.

Adverse Event Severity and Relationship to Study Drug

The investigator will use the following definitions to rate the severity of each adverse event:

Mild: The adverse event is transient and easily tolerated by the subject.

Moderate: The adverse event causes the subject discomfort and interrupts the subject's usual activities.

Severe: The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Reasonable Possibility: After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.

No Reasonable Possibility: After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

Pregnancy

While not an adverse event, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4). If a pregnancy occurs in a study subject, information regarding the pregnancy and the outcome will be collected.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered an SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

6.2 Other Safety Data Collection

Disease-Related Events

Abnormal laboratory, diagnostic procedural, or physical examination findings related to the disease under study will not be captured as an adverse event, unless the investigator deemed appropriate. Findings such as progression of pubertal staging are not considered to be adverse events but should be recorded in the subject's source documents and appropriate eCRF.

Drug-Related Events

LA is known to cause gonadotropins and sex steroids to temporarily rise above baseline levels because of the stimulatory effects of the drug within the first several weeks following initial administration. Therefore, an increase in clinical signs and symptoms, such as menses or spotting in females and behavioral changes in males, may occur at this time. These events should be recorded in the subject's source documents and appropriate eCRF.

The investigator will assess the subject for any LA-related symptoms at office visits or during parent or legal guardian phone calls that occur after each injection of study drug, whether expected or

unexpected; any worsening of pre-existing conditions (such as rapid progression of CPP symptoms) will be reviewed to determine whether they should be reported as adverse events.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

Complete and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the database lock. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

At the end of Part 1, an analysis of the primary, secondary, and other efficacy variables that were 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 only include data collected during Part 1 and will not include data collected during Part 2 or during the Follow-Up Period. The database will be versioned for an interim soft lock and any discrepant data will be clarified before the versioning. AbbVie will perform the analyses.

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.

7.2 Definition for Analysis Populations

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.

7.3 Statistical Analyses for Efficacy

Primary 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. 95% confidence interval based on the binomial distribution (Clopper-Pearson exact method) will be provided for the primary efficacy endpoint.

Additional details on the primary and other efficacy analyses are provided in the SAP.

Sample Size Estimation

No formal sample size calculation was performed. Based on previous studies and historical precedent that was 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.

7.4 Statistical Analyses for Safety

Analysis of safety will be detailed in the SAP.

8 ETHICS

8.1 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct, and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in [Appendix B](#).

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s).

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits to ensure human subject protection and reliability of study results. Data will be

generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

The end-of-study is defined as the date of the last subject's last visit or the actual date of follow-up contact, whichever is later.

12 REFERENCES

1. Badaru A, Wilson DM, Bachrach LK, et al. Sequential comparisons of one-month and three-month depot leuprolide regimens in central precocious puberty. *J Clin Endocrinol Metab.* 2006;91(5):1862-7.
2. Lee PA, Klein K, Mauras N, et al. Efficacy and safety of leuprolide acetate 3-month depot 11.25 milligrams or 30 milligrams for the treatment of central precocious puberty. *J Clin Endocrinol Metab.* 2012;97(5):1572-80.
3. Lee PA, Klein K, Mauras N, et al. 36-month treatment experience of two doses of leuprolide acetate 3-month depot for children with central precocious puberty. *J Clin Endocrinol Metab.* 2014;99(9):3153-9.
4. Brown RT. Adolescent growth and development. In: Holland-Hall C, Brown RT, editors. *Adolescent Medicine Secrets.* Philidephia, PA: Hanley & Belfus; 2002. p. 21-8.
5. Travers S, Slover R. Disorders of Puberty. In: MTM, editor. *Endocrine Secrets.* 4th ed. Philadelphia, PA: 2005. p. 354-67.
6. Carel JC, Eugster EA, Rogol A, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics.* 2009;123(4):e752-62.

APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
ACTH	adrenocorticotropic hormone
AOC	acute-on-chronic
ATEMS	AbbVie Temperature Excursion Management System
Beta-hCG	beta human chorionic gonadotropin
BMI	body mass index
CAH	congenital adrenal hyperplasia
CDSM	clinical drug supply management
COVID-19	Corona virus disease 2019
CPP	central precocious puberty
CRO	contract research organization
CT	computed axial tomography
DFP	direct-from-patient
DHEA	dehydroepiandrosterone
DTP	direct-to-patient
eCRF	electronic case report form
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GnRH	gonadotropin-releasing hormone
GnRHa	gonadotropin-releasing hormone agonist
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGF-1	insulin-like growth factor-1
IM	intramuscular
IRB	Institutional Review Board
IRT	Interactive response technology
LA	leuprolide acetate
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
PedsQL	Pediatric Quality of Life Inventory



PRO	patient-reported outcome
PROMIS	Patient Reported Outcomes Measurement Information System
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SUSAR	Suspected Unexpected Serious Adverse Reactions
TA MD	AbbVie therapeutic area medical director
US	United States

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M16-904: A Phase 3, Multicenter, 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 (CPP)

Protocol Date: 05 August 2020

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
1. Personally conducting or supervising the described investigation(s).
2. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
3. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
4. Reading the information in the approved full US Prescribing Information/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
5. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
6. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
7. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
8. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
9. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator

Date

Name of Principal Investigator (printed or typed)

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[REDACTED]	Executive Medical Director	General Medicine Clinical Development
[REDACTED]	Senior Director	Statistics Therapeutic Area Head
[REDACTED]	Medical Director	General Medicine Clinical Development
[REDACTED]	Principal Medical Writer	Medical Writing
[REDACTED]	Program Lead I	Clinical Program Development
[REDACTED]	Director	Clinical Pharmacokinetics and Pharmacodynamics
[REDACTED]	Director	Data and Statistical Sciences

APPENDIX D. ACTIVITY SCHEDULE

The required activities across subject encounters are shown in the following tables. Individual activities are described in detail in the **Operations Manual**. Week 48 is the end of Part 1 and also the start of Part 2. Week 48 activities for each part are identified in the tables below. Week 48 activities that end Part 1 are those that precede the third dose of LA 45 mg 6-month.

Study Activities Table (Screening and Part 1)

Activity	Screening (up to 4 weeks)	Part 1											
		Baseline (Day 1)	Day 2 (phone call)	Week 1	Week 4	Week 12	Week 20	Week 24	Week 24 + 48 hrs post injection	Week 24 + 7 days (phone call)	Week 32 (phone call)	Week 40 (phone call)	Week 44
□ INTERVIEWS & QUESTIONNAIRES													
Informed consent/assent	✓												
Eligibility criteria	✓	✓											
Medical and CPP history	✓	✓											
Family history (parental height and age of puberty onset)	✓	✓											
Menstrual history (females)	✓	✓											
Menstrual bleeding calendar (females)	✓	✓			✓	✓	✓	✓				✓	✓
Hormonal flare and AOC response assessment		✓	✓	✓	✓			✓	✓	✓			
LA 45 mg Injection site reaction assessment		✓	✓					✓	✓				

Activity	Screening (up to 4 weeks)	Part 1											
		Baseline (Day 1)	Day 2 (phone call)	Week 1	Week 4	Week 12	Week 20	Week 24	Week 24 + 48 hrs post injection	Week 24 + 7 days (phone call)	Week 32 (phone call)	Week 40 (phone call)	Week 44
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PedsQL and PROMIS questionnaires		✓				✓	✓						✓
LABORATORY TESTS & EXAMINATIONS													
Safety laboratory tests (chemistry, hematology)	✓	✓				✓		✓					✓
Urinalysis	✓												
Pregnancy test (females) (if applicable)	✓ (serum)	✓ (urine)											
Adrenal steroids	✓												
ACTH stimulation test (if applicable)	✓												
Beta-hCG (males)	✓												
GnRHa stimulation test	✓				✓	✓	✓	✓				✓	✓
Blood collection for estradiol (females)/testosterone (males)	✓	✓		✓	✓	✓	✓	✓	✓			✓	✓
Blood collection for LH and FSH	✓	✓		✓	✓	✓	✓	✓	✓			✓	✓
Blood collection for leuprolide concentration in first 20 subjects		✓		✓	✓	✓	✓	✓				✓	✓
Bone age radiograph	✓							✓					✓
MRI or CT scan (brain)	✓												

Activity	Screening (up to 4 weeks)	Part 1											
		Baseline (Day 1)	Day 2 (phone call)	Week 1	Week 4	Week 12	Week 20	Week 24	Week 24 + 48 hrs post injection	Week 24 + 7 days (phone call)	Week 32 (phone call)	Week 40 (phone call)	Week 44
Adrenal (all subjects) and testicular (males) ultrasound	✓												
Transdermal pelvic ultrasound (uterine and ovarian volume in females)	✓							✓					✓
Height (triplicate) and weight	✓	✓			✓	✓	✓	✓				✓	✓
Complete physical examination and vital signs	✓							✓					✓
Brief physical examination and vital signs		✓		✓	✓	✓	✓					✓	
Pubertal staging modified Tanner (all subjects)	✓							✓					✓
Penile length and width and testicular length and volume (males)	✓							✓					✓
Rx TREATMENT													
LA 45 mg 6-month depot formulation IM injection			✓						✓				

Study Activities Table (Part 2, Premature Discontinuation, Follow-Up Period, and Unscheduled Visit(s))

Activity	Part 2															Premature Discontinuation	12-week Follow-up phone call	Unscheduled Visit(s)	
	Week 48 (start of Part 2)	Week 48+1 day (phone call)	Week 48+48 hrs post injection	Week 48+ 7 days (phone call)	Week 72	Week 72+1 day (phone call)	Week 72+48 hrs post injection	Week 72+ 7 days (phone call)	Week 96	Week 96+1 day (phone call)	Week 96+48 hrs post injection	Week 96+ 7 days (phone call)	Week 120	Week 120+1 day (phone call)	Week 120+48 hrs post injection	Week 120+ 7 days (phone call)			
INTerviews & Questionnaires																			
Hormonal flare and AOC response assessment Note: Half of the subjects will be randomly selected (R) for AOC biochemical assessment 48 hours after injection of study drug at applicable visits. Other subjects (O) will have phone contacts 1 day after injection of study drug at applicable visits.	✓	✓ (O)	✓ (R)	✓	✓	✓ (O)	✓ (R)	✓	✓	✓ (O)	✓ (R)	✓	✓	✓ (O)	✓ (R)	✓			
LA 45 mg Injection site reaction assessment	✓	✓	✓		✓	✓	✓		✓	✓	✓		✓	✓	✓	✓			
Menstrual bleeding calendar (females)					✓				✓				✓				✓	✓	
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
PedsQL and PROMIS questionnaires					✓				✓				✓				✓	✓	
Laboratory Tests & Examinations																			
Safety laboratory tests (chemistry, hematology)						✓				✓				✓			✓	✓	✓
GnRHa stimulation test					✓				✓				✓			✓	✓	✓	

Activity	Part 2														Premature Discontinuation	12-week Follow-up phone call	Unscheduled Visit(s)
	Week 48 (start of Part 2)	Week 48 + 1 day (phone call)	Week 48 + 48 hrs post injection	Week 48 + 7 days (phone call)	Week 72	Week 72 + 1 day (phone call)	Week 72 + 48 hrs post injection	Week 72 + 7 days (phone call)	Week 96	Week 96 + 1 day (phone call)	Week 96 + 48 hrs post injection	Week 96 + 7 days (phone call)	Week 120	Week 120 + 1 day (phone call)	Week 120 + 48 hrs post injection	Week 120 + 7 days (phone call)	Week 144
Blood collection for estradiol (females)/testosterone (males) Note: samples obtained 48 hr post-injection only apply to subjects randomly assigned (R) to AOC biochemical evaluation by IRT at the beginning of Part 2.			✓ (R)		✓		✓ (R)		✓	✓ (R)				✓	✓ (R)		✓
Blood collection for LH and FSH Note: samples obtained 48 hr post-injection only apply to subjects randomly assigned (R) to AOC biochemical evaluation by IRT at the beginning of Part 2.			✓ (R)		✓		✓ (R)		✓	✓ (R)				✓	✓ (R)		✓
Blood collection for leuprolide concentration in first 20 subjects Note: applicable to subjects who discontinue prematurely during Part 1 only																	✓
Bone age radiograph					✓			✓			✓			✓		✓	✓
Transdermal pelvic ultrasound (uterine and ovarian volume in females)					✓			✓			✓			✓		✓	✓
Height (triplicate) and weight					✓			✓			✓			✓		✓	✓
Complete physical examination and vital signs					✓			✓			✓			✓		✓	✓

Activity	Part 2												Premature Discontinuation	12-week Follow-up phone call	Unscheduled Visit(s)
	Week 48 (start of Part 2)	Week 48 + 1 day (phone call)	Week 48 + 48 hrs post injection	Week 48 + 7 days (phone call)	Week 72	Week 72 + 1 day (phone call)	Week 72 + 48 hrs post injection	Week 72 + 7 days (phone call)	Week 96	Week 96 + 1 day (phone call)	Week 96 + 48 hrs post injection	Week 96 + 7 days (phone call)			
Brief physical examination and vital signs															✓
Pubertal staging modified Tanner (all subjects)					✓				✓				✓	✓	✓
Penile length and width and testicular length and volume (males)					✓				✓				✓	✓	✓
Rx TREATMENT															
LA 45 mg 6-month depot formulation IM injection	✓				✓				✓				✓		

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Version

Protocol	Date
Version 1.0	08 December 2017
Version 2.0	27 June 2018

The purpose of this amendment is primarily to provide alternative study procedures related to subject safety in response to the COVID-19 pandemic. Other administrative revisions and clarifications, as well as template update and typographical corrections were made throughout the protocol.

Alternative study procedures related to subject safety in response to the COVID-19 pandemic were added to the following sections:

Protocol

Section 4.1

Section 5.6

Operations Manual

Section 2

Section 3.8

Section 3.13

Section 3.14

Section 3.15

Section 3.19

Section 3.20

Section 4.2

Section 6.1

Section 6.4



APPENDIX F. OPERATIONS MANUAL

Operations Manual for Clinical Study Protocol M16-904

Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of Leuprolide Acetate 45 mg 6-month formulation in Children with Central Precocious Puberty

SPONSOR: AbbVie Inc.

ABBVIE INVESTIGATIONAL PRODUCT: Leuprolide acetate

FULL TITLE: A Phase 3, Multicenter, 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 (CPP)

1 CONTACTS

Sponsor/Emergency	[REDACTED] MD	Office: [REDACTED]
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Therapeutic Area	[REDACTED]	Fax: [REDACTED]
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SAE Reporting outside of RAVE	Pharmacovigilance	Fax: +1 847-938-0660 Email: PPDINDPharmacovigilance @abbvie.com
Protocol Deviations	[REDACTED] AbbVie Inc. Study Management Associate III 1 North Waukegan Road North Chicago, IL 60064	Office: [REDACTED] Mobile: [REDACTED] Email: [REDACTED]
OR		
	[REDACTED] AbbVie Inc. Study Project Manager II 1 North Waukegan Road North Chicago, IL 60064	Office: [REDACTED] Mobile: [REDACTED] Fax: [REDACTED] Email: [REDACTED]
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Bone Age Imaging

PAREXEL International, LLC
195 West Street
Waltham, MA 02451

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2 PROTOCOL ACTIVITIES BY VISIT

A list of activities performed during each visit, organized by visit, is presented in this section. Unscheduled visits may occur at any time as deemed appropriate by the investigator.

Activities are grouped by category (Interview, Exam, etc.). Further information about each activity is provided in Section 3.

If a subject cannot come to the site because of an unforeseen circumstance (e.g., the COVID-19 pandemic), study visits may be conducted virtually by site staff (e.g., by phone or video) or by a qualified home healthcare nurse in a non-hospital/clinic environment (e.g., the subject's home) at the request of the investigator and with the agreement of the subject's parent or legal guardian. AbbVie should be notified if this occurs, and the respective COVID-19 electronic case report forms (eCRFs) should be completed if applicable. Any visits conducted virtually or partially should be recorded as such on the respective COVID-19 eCRFs if applicable.

2.1 Individual Treatment Period Visit Activities (Screening and Part 1)

SCREENING VISIT:^a

 INTERVIEW	<ul style="list-style-type: none"> Informed consent/assent Eligibility criteria^b Medical and central precocious puberty (CPP) history Family history (parental height and age of puberty onset)^c Menstrual history (females) 	<ul style="list-style-type: none"> Menstrual bleeding calendar (females) Adverse event assessment Prior and concomitant therapy
 EXAM	<ul style="list-style-type: none"> Bone age radiograph Magnetic resonance imaging (MRI) or computed axial tomography (CT) scan (brain) Adrenal (all subjects) and testicular (males) ultrasound Height (in triplicate) and weight Complete physical examination Vital signs 	<ul style="list-style-type: none"> Pubertal staging (modified Tanner) (all subjects) Penile length and width and testicular length and volume (males) Transdermal pelvic ultrasound (uterine and ovarian volume) (females)
 LAB	<ul style="list-style-type: none"> Safety laboratory tests (hematology and chemistry) Urinalysis Adrenal steroids Adrenocorticotrophic hormone (ACTH) stimulation test (if applicable)^d Beta-human chorionic gonadotropin (beta-hCG) (males) 	<ul style="list-style-type: none"> Serum pregnancy test (females) (if applicable) Estradiol (females) Testosterone (males) Gonadotropin-releasing hormone agonist (GnRHa) stimulation test Luteinizing hormone (LH) and follicle-stimulating hormone (FSH)

- The Screening Period may be extended in certain circumstances (e.g., pending laboratory test results) following consultation with the sponsor.
- The results of certain retrospective procedures that were performed prior to informed consent that are considered standard of care and/or part of establishing a diagnosis of CPP and that are used to establish eligibility for this study, may be used if the procedure was performed within the specified retrospective windows, as allowed by the protocol. See Section 3.2.
- Parental actual height and age of puberty onset will be collected for both the birth mother and biological father, when available. It is recommended that the actual heights of both parents be measured in triplicate, if possible, at the site by the study staff using stadiometry equipment. Otherwise measurements of actual height as reported will be captured. See Section 3.4.
- The ACTH stimulation test is not required if CAH and adrenal disorders have been ruled out as per investigator's evaluation and results of previous or basal adrenal steroid testing. If the screening CAH panel results are inconclusive as per

investigator's judgment, subjects should have the ACTH stimulation test performed during the Screening period and prior to study drug administration. See Section 3.17.

DAY 1 VISIT (BASELINE):

 INTERVIEW	<ul style="list-style-type: none"> Eligibility criteria Update medical and CPP history Update family history (parental height and age of puberty onset)^a Update menstrual history (females) Hormonal flare and acute-on-chronic (AOC) response assessment Menstrual bleeding calendar (females) Adverse event assessment Concomitant therapy Leuprolide acetate (LA) 45 mg injection site reaction assessment
 PRO	<ul style="list-style-type: none"> Pediatric Quality of Life Inventory (PedsQL) and Patient Reported Outcomes Measurement Information System (PROMIS) questionnaires
 EXAM	<ul style="list-style-type: none"> Height (in triplicate) and weight Brief physical examination Vital signs
 LAB	<ul style="list-style-type: none"> Safety laboratory tests (hematology and chemistry) Urine pregnancy test (females) (if applicable) Estradiol (females) Testosterone (males) LH and FSH Leuprolide concentration (first 20 subjects only)
 TREATMENT	<ul style="list-style-type: none"> LA 45 mg 6-month

a. Parental actual height and age of puberty onset will be collected for both the birth mother and biological father, when available. It is recommended that the actual heights of both parents be measured in triplicate, if possible, at the site by the study staff using stadiometry equipment. Otherwise measurements of actual height as reported will be captured. See Section 3.4.

DAY 2 PHONE CALL (\pm 1 day) TO PARENT OR LEGAL GUARDIAN:

 INTERVIEW	<ul style="list-style-type: none"> Hormonal flare and acute-on-chronic (AOC) response assessment Adverse event assessment Concomitant therapy LA 45 mg injection site reaction assessment
--	---

WEEK 1 VISIT (\pm 3 days):

 INTERVIEW	<ul style="list-style-type: none"> Hormonal flare and AOC response assessment Adverse event assessment Concomitant therapy
 EXAM	<ul style="list-style-type: none"> Brief physical examination Vital signs
 LAB	<ul style="list-style-type: none"> Estradiol (females) Testosterone (males) LH and FSH Leuprolide concentration (first 20 subjects only)

WEEK 4 VISIT (\pm 6 days):

 INTERVIEW	<ul style="list-style-type: none"> Menstrual bleeding calendar (females) Adverse event assessment Concomitant therapy
 EXAM	<ul style="list-style-type: none"> Height (in triplicate) and weight Brief physical examination Vital signs
 LAB	<ul style="list-style-type: none"> Estradiol (females) Testosterone (males) LH and FSH GnRHa stimulation test Leuprolide concentration (first 20 subjects only)

WEEK 12 VISIT (\pm 6 days):

 INTERVIEW	<ul style="list-style-type: none"> Menstrual bleeding calendar (females) Adverse event assessment Concomitant therapy
 PRO	<ul style="list-style-type: none"> PedsQL and PROMIS questionnaires
 EXAM	<ul style="list-style-type: none"> Height (in triplicate) and weight Brief physical examination Vital signs
 LAB	<ul style="list-style-type: none"> Safety laboratory tests (hematology and chemistry) Estradiol (females) Testosterone (males) GnRHa stimulation test LH and FSH Leuprolide concentration (first 20 subjects only)

WEEK 20 VISIT (\pm 6 days):

 INTERVIEW	<ul style="list-style-type: none"> Menstrual bleeding calendar (females) Adverse event assessment Concomitant therapy
 EXAM	<ul style="list-style-type: none"> Height (in triplicate) and weight Brief physical examination Vital signs
 LAB	<ul style="list-style-type: none"> Estradiol (females) Testosterone (males) LH and FSH GnRHa stimulation test Leuprolide concentration (first 20 subjects only)

Week 24 VISIT (\pm 6 days):

 INTERVIEW	<ul style="list-style-type: none"> Hormonal flare and AOC response assessment Menstrual bleeding calendar (females) Adverse event assessment Concomitant therapy LA 45 mg injection site reaction assessment
 PRO	<ul style="list-style-type: none"> PedsQL and PROMIS questionnaires
 EXAM	<ul style="list-style-type: none"> Bone age radiograph Height (in triplicate) and weight Complete physical examination Vital signs Pubertal staging (modified Tanner) (all subjects) Penile length and width and testicular length and volume (males) Transdermal pelvic ultrasound (uterine and ovarian volume) (females)
 LAB	<ul style="list-style-type: none"> Safety laboratory tests (hematology and chemistry) Estradiol (females) Testosterone (males) GnRHa stimulation test LH and FSH Leuprolide concentration (first 20 subjects only)
 TREATMENT	<ul style="list-style-type: none"> LA 45 mg 6-month

WEEK 24 + 48 HOURS VISIT (\pm 24 hours) (48 HOURS POST INJECTION):

 INTERVIEW	<ul style="list-style-type: none"> Hormonal flare and AOC response assessment Adverse event assessment Concomitant therapy LA 45 mg injection site reaction assessment
 LAB	<ul style="list-style-type: none"> LH and FSH Estradiol (females) Testosterone (males)

WEEK 24 + 7 DAYS PHONE CALL (\pm 2 days) TO PARENT OR LEGAL GUARDIAN:

 INTERVIEW	<ul style="list-style-type: none"> • Hormonal flare and AOC response assessment • Adverse event assessment • Concomitant therapy
--	---

WEEK 32 (\pm 6 days) and WEEK 40 (\pm 6 days) PHONE CALLS TO PARENT OR LEGAL GUARDIAN:

 INTERVIEW	<ul style="list-style-type: none"> • Adverse event assessment • Concomitant therapy
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WEEK 44 VISIT (\pm 6 days):

 INTERVIEW	<ul style="list-style-type: none"> • Menstrual bleeding calendar (females) • Adverse event assessment • Concomitant therapy
 EXAM	<ul style="list-style-type: none"> • Height (in triplicate) and weight • Brief physical examination • Vital signs
 LAB	<ul style="list-style-type: none"> • Estradiol (females) • Testosterone (males) • LH and FSH • Leuprolide concentration (first 20 subjects only) • GnRHa stimulation test

Week 48 VISIT (\pm 6 days):

END OF PART 1^a

 INTERVIEW	<ul style="list-style-type: none"> • Menstrual bleeding calendar (females) • Adverse event assessment • Concomitant therapy
 PRO	<ul style="list-style-type: none"> • PedsQL and PROMIS questionnaires
 EXAM	<ul style="list-style-type: none"> • Bone age radiograph • Height (in triplicate) and weight • Complete physical examination • Vital signs • Pubertal staging (modified Tanner) (all subjects) • Penile length and width and testicular length and volume (males) • Transdermal pelvic ultrasound (uterine and ovarian volume) (females)
 LAB	<ul style="list-style-type: none"> • Safety laboratory tests (hematology and chemistry) • Estradiol (females) • Testosterone (males) • GnRHa stimulation test • LH and FSH • Leuprolide concentration (first 20 subjects only)

a. Week 48 is the end of Part 1 and the start of Part 2.

2.2 Individual Treatment Period Visit Activities (Part 2)

Week 48 VISIT (\pm 6 days):

START OF PART 2^{a,b}

 INTERVIEW	<ul style="list-style-type: none"> • Hormonal flare and acute-on-chronic (AOC) response assessment • Leuprolide acetate (LA) 45 mg injection site reaction assessment
 TREATMENT	<ul style="list-style-type: none"> • LA 45 mg 6-month

a. Week 48 is the end of Part 1 and the start of Part 2.
b. At the beginning of Part 2, using the interactive response technology (IRT) system, half of the subjects will be randomly selected to have visits for AOC biochemical assessment 48 hours after the injection of study drug at Weeks 48, 72, 96, and 120. Subjects who are not randomly selected for the AOC biochemical assessments will have phone contacts 1 day after the injection of study drug at Weeks 48, 72, 96, and 120.

WEEK 48 + 1 DAY PHONE CALL (\pm 2 days) TO PARENT OR LEGAL GUARDIAN:^a

 INTERVIEW	<ul style="list-style-type: none"> • Hormonal flare and AOC response assessment • Adverse event assessment • Concomitant therapy • LA 45 mg injection site reaction assessment
a. Does not apply to those subjects who are randomly selected for AOC biochemical assessment.	

WEEK 48 + 48 HOURS VISIT (\pm 24 hours) (48 HOURS POST INJECTION):^a

 INTERVIEW	<ul style="list-style-type: none"> • Hormonal flare and AOC response assessment • Adverse event assessment • Concomitant therapy • LA 45 mg injection site reaction assessment
 LAB	<ul style="list-style-type: none"> • Luteinizing hormone (LH) and Follicle-stimulating hormone (FSH) • Estradiol (females) • Testosterone (males)
a. Applies only to subjects who are randomly selected for AOC biochemical assessment.	

WEEK 48 + 7 DAYS PHONE CALL (\pm 2 days) TO PARENT OR LEGAL GUARDIAN:

 INTERVIEW	<ul style="list-style-type: none"> • Hormonal flare and AOC response assessment • Adverse event assessment • Concomitant therapy
--	---

WEEK 72 VISIT (\pm 6 days):

 INTERVIEW	<ul style="list-style-type: none"> • Hormonal flare and AOC response assessment • Menstrual bleeding calendar (females) • Adverse event assessment • Concomitant therapy • LA 45 mg injection site reaction assessment
 PRO	<ul style="list-style-type: none"> • Pediatric Quality of Life Inventory (PedSQL) and Patient Reported Outcomes Measurement Information System (PROMIS) questionnaires
 EXAM	<ul style="list-style-type: none"> • Bone age radiograph • Height (in triplicate) and weight • Complete physical examination • Vital signs • Pubertal staging (modified Tanner) (all subjects) • Penile length and width and testicular length and volume (males) • Transdermal pelvic ultrasound (uterine and ovarian volume) (females)
 LAB	<ul style="list-style-type: none"> • Safety laboratory tests (hematology and chemistry) • Estradiol (females) • Testosterone (males) • Gonadotropin-releasing hormone agonist (GnRHa) stimulation test • LH and FSH
 TREATMENT	<ul style="list-style-type: none"> • LA 45 mg 6-month

WEEK 72 + 1 DAY PHONE CALL (\pm 2 days) TO PARENT OR LEGAL GUARDIAN:^a

 INTERVIEW	<ul style="list-style-type: none"> • Hormonal flare and AOC response assessment • Adverse event assessment • Concomitant therapy • LA 45 mg injection site reaction assessment
--	--

a. Does not apply to those subjects who are randomly selected for AOC biochemical assessment.

WEEK 72 + 48 HOURS VISIT (\pm 24 hours) (48 HOURS POST INJECTION):^a

 INTERVIEW	<ul style="list-style-type: none"> • Hormonal flare and AOC response assessment • Adverse event assessment • Concomitant therapy • LA 45 mg injection site reaction assessment
 LAB	<ul style="list-style-type: none"> • LH and FSH • Estradiol (females) • Testosterone (males)

a. **Applies only to subjects who are randomly selected for AOC biochemical assessment.**

WEEK 72 + 7 DAYS PHONE CALL (\pm 2 days) TO PARENT OR LEGAL GUARDIAN:

 INTERVIEW	<ul style="list-style-type: none"> • Hormonal flare and AOC response assessment • Adverse event assessment • Concomitant therapy
--	---

WEEK 96 VISIT (\pm 6 days):

 INTERVIEW	<ul style="list-style-type: none"> • Hormonal flare and AOC response assessment • Menstrual bleeding calendar (females) • Adverse event assessment • Concomitant therapy • LA 45 mg injection site reaction assessment
 PRO	<ul style="list-style-type: none"> • PedsQL and PROMIS questionnaires
 EXAM	<ul style="list-style-type: none"> • Bone age radiograph • Height (in triplicate) and weight • Complete physical examination • Vital signs • Pubertal staging (modified Tanner) (all subjects) • Penile length and width and testicular length and volume (males) • Transdermal pelvic ultrasound (uterine and ovarian volume) (females)
 LAB	<ul style="list-style-type: none"> • Safety laboratory tests (hematology and chemistry) • Estradiol (females) • Testosterone (males) • GnRHa stimulation test • LH and FSH
 TREATMENT	<ul style="list-style-type: none"> • LA 45 mg 6-month

WEEK 96 + 1 DAY PHONE CALL (\pm 2 days) TO PARENT OR LEGAL GUARDIAN:^a

 INTERVIEW	<ul style="list-style-type: none">• Hormonal flare and AOC response assessment• Adverse event assessment• Concomitant therapy• LA 45 mg injection site reaction assessment
a. Does not apply to those subjects who are randomly selected for AOC biochemical assessment.	

WEEK 96 + 48 HOURS VISIT (\pm 24 hours) (48 HOURS POST INJECTION):^a

 INTERVIEW	<ul style="list-style-type: none">• Hormonal flare and AOC response assessment• Adverse event assessment• Concomitant therapy• LA 45 mg injection site reaction assessment
 LAB	<ul style="list-style-type: none">• LH and FSH• Estradiol (females)• Testosterone (males)
a. Applies only to subjects who are randomly selected for AOC biochemical assessment.	

WEEK 96 + 7 DAYS PHONE CALL (\pm 2 days) TO PARENT OR LEGAL GUARDIAN:

 INTERVIEW	<ul style="list-style-type: none">• Hormonal flare and AOC response assessment• Adverse event assessment• Concomitant therapy
--	---

WEEK 120 VISIT (\pm 6 days):

 INTERVIEW	<ul style="list-style-type: none"> • Hormonal flare and AOC response assessment • Menstrual bleeding calendar (females) • Adverse event assessment • Concomitant therapy • LA 45 mg injection site reaction assessment
 PRO	<ul style="list-style-type: none"> • PedsQL and PROMIS questionnaires
 EXAM	<ul style="list-style-type: none"> • Bone age radiograph • Height (in triplicate) and weight • Complete physical examination • Vital signs • Pubertal staging (modified Tanner) (all subjects) • Penile length and width and testicular length and volume (males) • Transdermal pelvic ultrasound (uterine and ovarian volume) (females)
 LAB	<ul style="list-style-type: none"> • Safety laboratory tests (hematology and chemistry) • Estradiol (females) • Testosterone (males) • GnRHa stimulation test • LH and FSH
 TREATMENT	<ul style="list-style-type: none"> • LA 45 mg 6-month

WEEK 120 + 1 Day PHONE CALL (\pm 2 days) TO PARENT OR LEGAL GUARDIAN:^a

 INTERVIEW	<ul style="list-style-type: none"> • Hormonal flare and AOC response assessment • Adverse event assessment • Concomitant therapy • LA 45 mg injection site reaction assessment
a. Does not apply to those subjects who are randomly selected for AOC biochemical assessment.	

WEEK 120 + 48 HOURS VISIT (\pm 24 hours) (48 HOURS POST INJECTION):^a

 INTERVIEW	<ul style="list-style-type: none"> • Hormonal flare and AOC response assessment • Adverse event assessment • Concomitant therapy • LA 45 mg injection site reaction assessment
 LAB	<ul style="list-style-type: none"> • LH and FSH • Estradiol (females) • Testosterone (males)
a. Applies only to subjects who are randomly selected for AOC biochemical assessment.	

WEEK 120 + 7 Days PHONE CALL (± 2 days) TO PARENT OR LEGAL GUARDIAN:

 INTERVIEW	<ul style="list-style-type: none"> • Hormonal flare and AOC response assessment • Adverse event assessment • Concomitant therapy
--	---

WEEK 144 VISIT (± 6 days):

 INTERVIEW	<ul style="list-style-type: none"> • Menstrual bleeding calendar (females) • Adverse event assessment • Concomitant therapy
 PRO	<ul style="list-style-type: none"> • PedsQL and PROMIS questionnaires
 EXAM	<ul style="list-style-type: none"> • Bone age radiograph • Height (in triplicate) and weight • Complete physical examination • Vital signs • Pubertal staging (modified Tanner) (all subjects) • Penile length and width and testicular length and volume (males) • Transdermal pelvic ultrasound (uterine and ovarian volume) (females)
 LAB	<ul style="list-style-type: none"> • Safety laboratory tests (hematology and chemistry) • Estradiol (females) • Testosterone (males) • GnRHa stimulation test • LH and FSH

PREMATURE DISCONTINUATION:

 INTERVIEW	<ul style="list-style-type: none"> • Menstrual bleeding calendar (females) • Adverse event assessment • Concomitant therapy
 PRO	<ul style="list-style-type: none"> • PedsQL and PROMIS questionnaires
 EXAM	<ul style="list-style-type: none"> • Bone age radiograph • Height (in triplicate) and weight • Complete physical examination • Vital signs • Pubertal staging (modified Tanner) (all subjects) • Penile length and width and testicular length and volume (males) • Transdermal pelvic ultrasound (uterine and ovarian volume) (females)
 LAB	<ul style="list-style-type: none"> • Safety laboratory tests (hematology and chemistry) • Estradiol (females) • Testosterone (males) • GnRHa stimulation test • LH and FSH • Leuprolide concentration (first 20 subjects only) (applicable to subjects who discontinue prematurely during Part 1 only)

UNSCHEDULED VISIT(S):

 INTERVIEW	<ul style="list-style-type: none">• Adverse event assessment• Concomitant therapy
 EXAM	<ul style="list-style-type: none">• Brief physical examination• Pubertal staging (modified Tanner) (all subjects)• Penile length and width and testicular length and volume (males)• Vital signs
 LAB	<ul style="list-style-type: none">• Safety laboratory tests (hematology and chemistry)• Estradiol (females)• Testosterone (males)• GnRHa stimulation test• LH and FSH

2.3 Individual Posttreatment Period Visit Activities

12-WEEK FOLLOW-UP PHONE CALL (\pm 6 days) TO PARENT OR LEGAL GUARDIAN:

 INTERVIEW	<ul style="list-style-type: none">• Adverse event assessment• Concomitant therapy
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3 STUDY PROCEDURES

3.1 Subject Information and Informed Consent and Assent

The investigator or his/her representative will explain the nature of the study to the subject's parent or legal guardian and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject or any medications being discontinued by the subject to participate in this study, the informed consent statement will be reviewed, signed, and dated by the subject's parent or legal guardian, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed informed consent will be given to the subject's parent or legal guardian, and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documentation to confirm that informed consent and assent were obtained prior to any study-related procedures and that the subject's parent or legal guardian received a signed copy. Each subject must review, understand, and sign the assent form when appropriate (as specified either by the institutional review board [IRB] and/or state and local regulations).

Information regarding benefits for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

Rules and regulations for the consent or assent process of minors differ among countries with participating principal investigators. The investigator is responsible for ensuring compliance with all applicable rules. In general, a subject who is a minor should be informed within the limits of his/her understanding and with age-appropriate words. When deemed necessary by the IRB, the documented assent for subjects who are minors must be obtained.

Where assent is required, the investigator or his/her representative will explain the nature of the study to the subject and the subject's parent/legal guardian and answer all questions regarding this study. Subjects will be included in all discussions in order to obtain verbal or written assent. Prior to any study-specific screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject's parent/legal guardian, the person who administered the informed consent, and any other signatories according to local requirements. Additionally, in keeping with each institution's IRB requirements, an informed assent form may also be obtained by each subject prior to any study-related procedures being performed. A copy of the informed consent form and the assent form will be given to the subject and the subject's parent/legal guardian, and the original will be placed in the subject's medical record. If a subject becomes of legal age during the course of the study, the consent procedure needs to be repeated.

3.2 Eligibility Criteria

Eligibility criteria will be assessed at Screening and on Day 1 (Baseline).

The results of certain retrospective procedures that were performed prior to informed consent that are considered standard of care and/or part of establishing a diagnosis of CPP, and that are used to establish eligibility for this study, may be used if the procedure was performed within the specified retrospective windows, as allowed by the protocol (see Section 3.15, Section 3.16, Section 3.18, and Sections 3.23 through 3.26). Any results from prior procedures or blood tests that were used to establish eligibility must be available in the subject's source file; if not available in the subject's source file, the required test/procedure will be repeated and results reviewed prior to the subject receiving the first injection of study drug.

3.3 Medical and CPP History

Medical History

A complete medical history will be taken at Screening. The subject's medical history will be updated at the Day 1 visit. This updated medical history will serve as the Baseline for clinical assessment. Medical history will include the subject's race, ethnicity, sex, and full date of birth; and a review of all major organ systems, including any history of cancer, diabetes mellitus, gastrointestinal, cardiac, neurologic (including any trauma to the central nervous system), pulmonary, immunodeficiency, hepatic, renal, endocrine, or other systems. The disease and condition will be captured, as well as date of onset and whether the disease/condition is ongoing.

CPP History

Medical history will also focus on the subject's history of CPP and will record the date of any sign of puberty first noticed, and the date first visit seen by a physician for CPP. The diagnostic test(s)

performed, the results, and progression of symptoms of CPP will be recorded. Whether the subject is naïve to gonadotropin-releasing hormone agonist (GnRHa) treatment or previously treated with a GnRHa, and any prior GnRHa medications used in the treatment of CPP will also be recorded. A historical height (at least 6 months prior to Screening) is needed, and if available, historical information on subject's annual growth (height and date of height measurement) will be collected.

3.4 Family History

Family history: parental actual height and age of puberty onset will be collected for both the birth mother and biological father, when available. It is recommended that the actual heights of both parents be measured in triplicate, if possible, at the site by the study staff using stadiometry equipment. Otherwise measurements of actual height as reported will be captured.

3.5 Menstrual History

A history of menstrual periods (female subjects), including date of first occurrence (menarche) will be collected. Refer to Section [3.22](#) for the menstrual bleeding calendar.

3.6 Adverse Event Assessment

Please refer to Section [4.1](#).

3.7 Prior and Concomitant Medications

Prior and concomitant medications will be assessed at the time points specified in Section [2](#).

3.8 Patient-Reported Outcomes

The subject's parent or legal guardian will complete the patient-reported outcome (PRO) instruments. The subject's parent or legal guardian should be instructed to follow the instructions provided with the instruments and to provide the best possible response to each item. The instrument that corresponds to the age at which the subject entered the study will be used throughout the study.

Site personnel shall not provide interpretation or assistance to subject or subject's parent or legal guardian other than encouragement to complete the tasks. Site personnel may read the questionnaires to the subject's parent or legal guardian who is functionally unable to read the instruments. Site personnel will encourage completion of the instruments at all specified visits (see Section [2](#)) and will ensure that a response is entered for all items.

If a subject cannot come to the site because of unforeseen circumstances (e.g., the COVID-19 pandemic), patient-reported outcome entries may be administered by site staff over the phone and responses collected on paper (source) and transcribed into electronic data capture (EDC) or entered by site staff directly into an electronic collection system. AbbVie should be notified if this occurs.

Two different PRO instruments will be used: Pediatric Quality of Life Inventory™ (PedsQL™) (all subjects) and Patient Reported Outcomes Measurement Information System (PROMIS) Peer Relationships (subjects 5 years of age and older):

- Ages 2 – 4 years:
 - PedsQL Parent Report for Toddlers (2 – 4 years).
- Ages 5 – 7 years:
 - PedsQL Parent Report for Young Child (5 – 7 years).
 - PROMIS Peer Relationships Guardian Proxy Format.
- Ages 8 – 12 years:
 - PedsQL Parent Report for Child (8 – 12 years).
 - PROMIS Peer Relationships Guardian Proxy format.

The information will be collected at Baseline and at Weeks 12, 24, 48, 72, 96, 120, and 144. This information will also be collected at the Discontinuation Visit if the subject discontinues the study prematurely.

3.9 Complete and Brief Physical Examinations

A complete or brief physical examination will be performed at the study visits specified in Section 2. Any significant physical examination findings after the first injection of study drug will be recorded as adverse events. All findings, whether related to an adverse event or part of each subject's medical history, will be captured on the appropriate eCRF page.

At any time, the investigator can perform a symptom-directed physical examination, as deemed necessary.

3.10 Pubertal Staging Modified Tanner

Pubertal staging will be assessed in all subjects using modified Tanner staging as described below. All data will be captured in the source documentation and entered into the appropriate eCRF.

Breast: (Female subjects) Breast development will be assessed for Stages 1 through 5.

Pubic Hair: (All subjects) Pubic hair will be assessed for Stages 1 through 5.

Genitalia: (Male subjects) Development of external genitalia will be assessed for Stages 1 through 5. Measurements to assess changes in testes and penile size will be captured and will include testicular length (centimeters) and volume (milliliters) measured via orchidometer (Prader beads) and penile length and width (centimeters).

The same individual, if possible, will rate pubertal staging for all subjects and for male subjects measure penile length and width and testicular length and volume at each designated study visit. Pubertal stage

will be rated according to Section 7.1 and Section 7.2, "Pubertal Stages Worksheet Male" and "Pubertal Stages Worksheet Female."

Progression of CPP-related symptoms are not to be documented in the adverse event eCRF but should be documented in Pubertal Staging eCRFs (for male or female subjects as applicable). Refer to Section 6.2 of the Protocol "Disease-Related Events" and Section 3.21 "Hormonal Flare and Acute-on-Chronic Response Assessment."

3.11 Height and Weight

Height and weight will be measured at the time points specified in Section 2.

AbbVie will calculate growth rate (centimeter/year), both prior to treatment in the study and during the study. Two measurements of height at least 6 months apart are needed for the baseline calculation. Thus, a historical height that was obtained at least 6 months prior to Screening will be recorded along with the date of measurement. Height should be measured in triplicate using standard stadiometer equipment, such as Harpenden stadiometer or recumbent length table. Height should be measured using the same measurement tools, and if possible, the same study staff member should be conducting the measurements at each study visit. Height will be recorded in the source documentation and captured in the eCRFs.

3.12 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse rate, body temperature (rectal, oral, aural, or axillary), and respiratory rate will be obtained at the visits specified in Section 2.

3.13 Clinical Laboratory Tests

A certified laboratory will be used to process and provide results for the clinical laboratory tests. Laboratory reference ranges will be obtained prior to the initiation of the study.

Instructions for the collection, processing, and shipping of these samples will be provided by the central laboratory listed in Section 1.

If a subject cannot visit the site because of unforeseen circumstances (e.g., the COVID-19 pandemic), samples may be collected by a home healthcare service and sent to the central laboratory. If the central laboratory cannot be used to test samples because of unforeseen circumstances (e.g., the COVID-19 pandemic), samples may be collected and tested at a local laboratory. AbbVie should be notified if any of those situations occur.

If a laboratory test value is outside the reference range and the investigator considers the laboratory test result to be clinically significant, the investigator will:

- repeat the test to verify the out-of-range value;
- follow the out-of-range value to a satisfactory clinical resolution; or

- discontinue the subject from the study or require the subject to receive treatment; in this case, the laboratory result will be recorded as an adverse event.

Clinical Laboratory Tests		
Hematology	Clinical Chemistry	Chorionic Gonadotropin, Human, β -hCG
CBC: RBC count and WBC count Hematocrit Hemoglobin Mean corpuscular hemoglobin MCHC Mean corpuscular volume Neutrophils Lymphocytes Monocytes Eosinophils Basophils Platelet count	Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Sodium Potassium Bicarbonate Chloride Calcium Creatinine Glucose Lactate dehydrogenase Magnesium Phosphorus Total bilirubin Direct bilirubin Indirect bilirubin Total protein Uric acid	Quantitative β -hCG (male subjects) Adrenal Steroids CAH pediatric panel: androstenedione, cortisol, DHEA, 17 OH-progesterone, total testosterone If initial screening results of CAH panel are inconclusive as per investigator's judgment, CAH panel may be repeated prior to and following an ACTH stimulation test.
Urine	Gonadotropins and Sex Steroids	
Macroscopic chemical analysis: color & clarity, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase Urinalysis, microscopic (if macroscopic analysis is abnormal)	<u>Basal and GnRHa-stimulated</u> LH FSH E2 (females) T (males)	

ACTH = adrenocorticotrophic hormone; β -hCG = beta human chorionic gonadotropin; CBC = complete blood count;
CAH = congenital adrenal hyperplasia; DHEA = dehydroepiandrosterone; E2 = estradiol; FSH = follicle-stimulating hormone; LH = luteinizing hormone; MCHC = mean corpuscular hemoglobin concentration; RBC = red blood cell; T = testosterone; WBC = white blood cell

Pregnancy Tests

For female subjects \geq 10 years of age, a serum pregnancy test will be performed at the central laboratory at Screening and a urine pregnancy test will be performed at the site on Day 1. For female subjects $<$ 10 years of age, pregnancy tests may be performed at the investigator's discretion. The pregnancy test must be negative before the first dose of study drug can be administered. Additional urine pregnancy tests may be performed at the discretion of the principal investigator.

Urinalysis

Urinalysis will be completed at all required visits. Specified abnormal macroscopic urinalyses defined as leukocytes, nitrite, protein, ketones, or blood greater than negative, or glucose greater than normal will be followed up with a microscopic analysis at the central laboratory.

3.14 Pharmacokinetic Blood Collection for Leuprolide Concentration

Blood samples will be collected in a subset of 20 subjects for leuprolide analysis to coincide with the GnRHa stimulation test time points when possible. Investigative sites will be notified when the pharmacokinetic subset has been fulfilled. Blood samples will be collected at the time points indicated in Section 2.

On Day 1, blood samples will be collected immediately prior to (0 minutes) and 30 (\pm 5) minutes and 60 (\pm 5) minutes after the leuprolide acetate (LA) 45 mg intramuscular injection. At Weeks 1, 4, 12, 20, 24 (time of second injection of study drug), 44, and 48 (time of third injection of study drug for subjects who continue to Part 2), subjects who are in the pharmacokinetic subset will return to the clinic for blood collection for leuprolide concentration. At visits where there is a GnRHa stimulation test, blood should be collected prior to the GnRHa stimulation test. At Week 24 and Week 48 (for subjects who continue to Part 2), the stimulation test is performed prior to the LA 45 mg injection. Blood draw for pharmacokinetics should only be performed at the premature discontinuation visit if the subject discontinues at any time during Part 1. For Part 1 of the study, 10 blood samples will be collected across study visits for the quantitation of serum leuprolide concentrations (see [Table 1](#)).

For each pharmacokinetic sample, a whole blood sample will be collected for serum leuprolide determination. Blood samples will be collected as close as possible to the specified times indicated in [Table 1](#). The pharmacokinetic samples should be collected at the same time as the samples are collected for serum testosterone, estradiol, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), when applicable. In each sample, leuprolide concentration will be determined with a validated method under the supervision of AbbVie. Refer to the Laboratory Manual for sample collection and shipment instructions.

If a subject who is participating in the pharmacokinetic subset cannot come to the site because of unforeseen circumstances (e.g., the COVID-19 pandemic), the pharmacokinetic samples collection may be performed by a home healthcare nurse at the subject's home. AbbVie should be notified if this occurs.

Table 1. Pharmacokinetic Blood Collection for Leuprolide

	Day 1 1st LA 45 mg Injection	Week 1	Weeks 4 – 20 (Each Visit)	Week 24 2nd LA 45 mg Injection	Weeks 44, 48, and Premature Discontinuation^{a,b}
Time Relative to:	Study drug Injection (no stimulation test)	No reference point (no stimulation test)	Stimulation Test	Stimulation Test	Stimulation Test
0 minutes (immediately before)	Leuprolide	Leuprolide	Leuprolide	Leuprolide	Leuprolide
30 (± 5) minutes after	Leuprolide	--	--	--	--
60 (± 5) minutes after	Leuprolide	--	--	--	--

LA = leuprolide acetate

a. Subjects who continue to Part 2 will receive their third LA 45 mg injection at Week 48.

b. A pharmacokinetic sample will also be collected for subjects who discontinue prematurely before Week 48.

Notes: The LA 45 mg injection must be administered after the last blood collection for the stimulation test.

3.15 GnRHa Stimulation Test and Blood Collection for Gonadotropin and Sex Steroid Concentrations

Blood samples for hormones and GnRHa stimulation tests will be conducted at the time points indicated in Section 2. GnRHa stimulation tests will be performed using an LA aqueous formulation at 20 µg/kg subcutaneous injection at the weeks indicated in Table 2. Injection site reactions to stimulation test should be documented in appropriate eCRF.

Table 2. GnRHa Stimulation Test and Blood Collection for Gonadotropins and Sex Steroids

Timing	Screening	Day 1		Week 1	Weeks 4 – 20		Week 24	Weeks 44, 48, 72, 96, 120, 144, and Premature Discontinuation
		1 st LA 45 mg Injection	Week 1		(Each Visit)	2 nd LA 45 mg Injection		
Time Relative to:	Stimulation Test	Study drug injection (no stimulation test)	No reference point (no stimulation test)	Stimulation Test	Stimulation Test	Study drug injection	Stimulation Test	Stimulation Test
0 minutes (immediately before)	LH, FSH, E2, T	LH, FSH, E2, T	LH, FSH, E2, T	LH, FSH, E2, T	LH, FSH, E2, T	--	LH, FSH, E2, T	
30 (± 5) minutes after	LH, FSH	LH, FSH	--	LH, FSH	LH, FSH	--	LH, FSH	
60 (± 5) minutes after	LH, FSH, E2, T	LH, FSH, E2, T	--	LH, FSH, E2, T	LH, FSH, E2, T	--	LH, FSH, E2, T	
48 hours after	--	--	--	--	--	LH, FSH, E2, T	--	

AOC = acute-on-chronic; E2 = estradiol; FSH = follicle-stimulating hormone; GnRHa = gonadotropin-releasing hormone agonist; LA = leuprolide acetate; LH = luteinizing hormone; T = testosterone

a. LH, FSH, E2, T must be obtained for AOC biochemical assessment.

b. Blood collection 48 hours after the injection of study drug at Weeks 48, 72, 96, and 120 applies only to those subjects who are randomly selected for AOC biochemical assessment.

Note: For visits with a stimulation test and a study drug injection, the study drug injection must be administered after the last blood collection for the stimulation test.

The GnRHa stimulation tests will be performed and blood samples will be collected for gonadotropins (LH, FSH) and sex steroids (estradiol in female subjects and testosterone in male subjects) as shown in Table 2. For samples that will be collected in reference to either the stimulation test or the LA 45 mg 6-month injection; the 0 minute samples are to be drawn immediately prior to their reference points. It is recommended that the stimulation test be performed preferably in the morning and as close to the same time at each visit as possible.

Subjects naïve to GnRHa treatment will not need to repeat a screening stimulation test if a stimulation test was performed within 1 month prior to the screening visit and a diagnosis of CPP was established. The agent (GnRHa) and dose used for the stimulation test, the test result, and the date performed will be captured in the source documentation and in the appropriate eCRF. Note: even when the Screening stimulation test is not required, a screening LH, FSH, testosterone (male) or estradiol (female) sample is still required.

Subjects previously treated with a GnRHa will have a stimulation test during Screening to demonstrate adequate LH suppression (LH < 4 mIU/mL) prior to receiving their first dose of study drug (LA 45 mg 6-month).

Dates and times of sample collection for these tests will be recorded in the source documentation and in the eCRFs.

During Screening, blood samples for LH, FSH, testosterone (in male subjects) or estradiol (in female subjects) will be collected and measured using a clinical laboratory test at the central laboratory identified in Section 3.13 to assess eligibility.

From Day 1 and onward, blood samples for LH and FSH (4 mL, which includes the blood volume for leuprolide) will be collected and shipped according to the instructions in the laboratory manual for the determination of LH and FSH following a validated method under the supervision of the sponsor, AbbVie.

From Day 1 and onward, 3-mL blood samples for testosterone (in male subjects) or estradiol (in female subjects) will be collected and shipped according to the instructions in the laboratory manual for the determination of testosterone and estradiol following a validated method under the supervision of the sponsor, AbbVie.

At Week 24 (and Weeks 48, 72, 96, and 120 for subjects who continue to Part 2), the LA 45 mg study drug injection must be administered after the last blood collection (60 minutes) for the stimulation test. If the Week 24 (and Weeks 48, 72, 96, and 120 for subjects who continue to Part 2) stimulation test results indicate inadequate peak LH suppression (≥ 4 mIU/mL), the subject may be asked to return to the clinic to be evaluated for signs/symptoms of puberty progression. If this occurs, the visit will be documented as an unscheduled visit. Unscheduled blood samples for basal or stimulated LH, FSH, testosterone (in male subjects), or estradiol (in female subjects) may be collected according to the investigator's clinical judgment at any time throughout the study and sent to the central laboratory for analysis and resulting.

If a subject cannot come to the site because of unforeseen circumstances (e.g., the COVID-19 pandemic), the GnRHa stimulation test and required gonadotropins and sex steroids blood samples collection may be performed by a home healthcare nurse at the subject's home. AbbVie should be notified if this occurs. Refer to the Laboratory Manual for sample collection instructions.

3.16 Adrenal Steroids

Adrenal steroid testing for all subjects to rule out congenital adrenal hyperplasia (CAH) will be performed at Screening, if not previously performed. If previously performed, the date and test result must be available in the source documentation. If the results are not available in the source documentation, the test must be repeated to establish eligibility. This testing (pediatric CAH panel) will include androstenedione, cortisol, dehydroepiandrosterone (DHEA), 17 OH-progesterone, and testosterone.

3.17 ACTH Stimulation Test

The ACTH stimulation test is not required if CAH and adrenal disorders have been ruled out as per investigator's evaluation and results of previous or basal adrenal steroid testing. If the screening CAH panel results are inconclusive as per investigator's judgment, subjects should have the

adrenocorticotropic hormone (ACTH) stimulation test performed during the Screening period and prior to study drug administration. The ACTH stimulation test procedure will be conducted per standard of care. Two blood samples, 0 minutes and 60 minutes after the intravenous injection of commercially available corticotropin, will be collected and sent to central laboratory for analysis of androstenedione, cortisol, DHEA, 17-OH-progesterone, and testosterone levels.

3.18 Beta-hCG (Male Subjects)

Beta human chorionic gonadotropin (β -hCG) levels to rule out a chorionic gonadotropin-secreting tumor will be performed for male subjects at Screening, unless performed prior to Screening. If previously performed, the date and test result must be available in the source documentation, or the assessment must be repeated to establish eligibility.

3.19 Administration of Study Drug

Study drug will be administered to subjects beginning at Baseline (Day 1) and at the time points specified in Section 2 as follows:

Part 1: LA 45 mg 6-month, given as a single intramuscular injection. The first injection will be administered on Day 1, and the second injection will be administered at Week 24.

For subjects who were previously treated with GnRHa therapy, the first injection of study drug should be administered at the end of the previous GnRHa treatment cycle.

Part 2: LA 45 mg 6-month, given as a single intramuscular injection at 24-week intervals (up to 24 months) starting at Week 48 until Week 120.

Study site staff will administer all injections of LA 45 mg 6-month. Each injection of study drug should be administered in the gluteal area, anterior thigh, or deltoid. Injection sites should be alternated to minimize injection site reactions.

If a subject cannot come to the site because of unforeseen circumstances (e.g., the COVID-19 pandemic), the injection of study drug may be administered by a home healthcare nurse at the subject's home. AbbVie should be notified if this occurs.

Refer to Section 7.3 for dose preparation instructions.

Depending on local regulations, provisioning of study drug and generic LA for stimulation test for direct-to-patient (DTP) and direct-from-patient (DFP) transfer because of unforeseen circumstances (e.g., the COVID-19 pandemic) will be available upon request. AbbVie should be notified if this occurs. Sites can use Marken, a third-party vendor with which AbbVie has an agreement, for drug shipment in these circumstances or sites may use a local courier.

Sites will be responsible for meeting IRB reporting requirements and submitting the booking form (which will be provided) to the local IRB (as applicable).

The investigator must discuss the DTP process with the subject's parent or legal guardian:

- Obtain consent to provide delivery information to Marken and/or local courier and record this in source documentation.
- Obtain and review results of required safety procedures as applicable before registering subject dispensation of study drug in interactive response technology (IRT).
- Confirm that the subject's parent or legal guardian will be available to accept delivery.
- The site will follow-up with the subject's parent or legal guardian after shipment is received.

Sites will be required to retain documentation of the shipment for investigational product accountability and monitoring.

3.20 LA 45 mg Injection Site Reaction Assessment

Study site staff (or home healthcare nurse if applicable) will assess the injection site on the day of the LA 45 mg injection prior to the subject leaving the investigative site. The time of the assessment (post injection) as well as a description of the injection site will be recorded in the source documentation and entered into the appropriate eCRF. At the Day 1 visit, the site will discuss with the parent or legal guardian how to assess the injection site and when a call to the investigative site is needed for clinical assessment. Additionally, the site will phone the parent or legal guardian or there will be an on-site visit (or a home healthcare visit if applicable) at the time points specified in Section 2 to obtain a description of the injection site. Refer to Section 7.4 for a sample of the Leuprolide Acetate 45 mg Injection Site Assessment Form. If required, the subject may be asked to come in to the clinic for an assessment, based on investigator discretion. A description of the injection site will be recorded in the source documentation and in the appropriate eCRF. All injection site reactions will be captured as adverse events. Any injection site reaction that reaches serious criteria as stated in Section 6.1 of the protocol will be captured as a serious adverse event (SAE) and reported as described in the protocol.

If a subject cannot come to the site because of unforeseen circumstances (e.g., the COVID-19 pandemic), and the injection of study drug was administered by a home healthcare nurse at the subject's home, the injection site reaction assessment may be conducted by the home healthcare nurse. AbbVie should be notified if this occurs.

3.21 Hormonal Flare and Acute-on-Chronic Response Assessment

Blood samples for AOC biochemical assessment of basal hormones (FSH, LH, and estradiol in females or testosterone in males) will be collected as follows:

Part 1: Week 1 and 48 hours after the second injection of LA 45 mg 6-month at Week 24 in all subjects enrolled.

Part 2: 48 hours after the injection of LA 45 mg 6-month at Weeks 48, 72, 96, and 120 in those subjects who are randomly selected for AOC biochemical assessment. Subjects will be randomly assigned to the AOC subgroup at Week 48 when the visit is registered in IRT.

Following each injection of LA 45 mg 6-month, the sites (or home healthcare nurse if applicable) will assess clinical signs and symptoms of hormonal flare and AOC response to an increase in sex steroids (e.g., breast tenderness and vaginal discharge in female subjects; frequent or prolonged erections, age-inappropriate behavior that may be sexual in nature in male subjects; or in both female and male subjects, exacerbation or acceleration of pubertal symptoms, substantial mood swings, or new symptoms). Sites (or home healthcare nurse if applicable) will assess for any events on the day of each study drug injection before the subject leaves the site. Sites will call the parent or legal guardian after each study drug injection at the time points specified in Section 2.

The site will record reported events in the source documentation and on the appropriate eCRF.

If unusual or unexpected clinical effects are reported during the phone call, or are spontaneously reported by the parent or legal guardian, subjects may be asked to return to the clinic at the investigator's discretion, and have a blood sample collected for AOC biochemical assessment of basal hormone levels (LH, FSH, and estradiol in females or testosterone in males). If this occurs, the visit will be documented as an Unscheduled Visit. Refer to Section 7.5 for a sample of the Hormonal Flare and Acute-on-Chronic Hormonal Response form.

When assessing these events, refer to Section 6.1 of the protocol.

3.22 Menstrual Bleeding Calendar (Female Subjects)

Information on menses will be collected as part of medical history for female subjects. Female subjects and/or their parent or legal guardian will be asked to record any menses that occurs from the time of signing the consent and assent form, through the end of study participation on a menstrual bleeding calendar. The site will train the subject (if deemed appropriate) and/or the parent or legal guardian on how to complete the menstrual bleeding calendar. The calendar will be distributed at the Screening visit and will be reviewed by the site at each subsequent study visit. Refer to Section 7.6.

The subject and/or parent or legal guardian will record only days with menstrual spotting or bleeding. All menstrual bleeding calendar entries must be captured in the appropriate eCRF.

3.23 Bone Age Radiograph

Bone age hand and wrist radiographs will be performed to assess bone maturation at Screening, unless performed within 3 months prior to Screening, and at the time points specified in Section 2. These radiographs will be performed at a facility specified by the study investigator and will be sent to an imaging vendor for Fels bone age measurement using the BoneXpert automated system. If a previous bone age radiograph is available from within 3 months prior to Screening and the radiograph meets the technical requirements of the imaging vendor, that radiograph may be used, and no additional bone age radiographs will be performed during the Screening Period. The bone age results will be used to assess subject eligibility.

3.24 Brain Magnetic Resonance Imaging or Computed Axial Tomography Scan

Magnetic resonance imaging (MRI) or computed axial tomography (CT) high resolution scan of the brain (including pituitary and hypothalamus), to rule out intracranial tumor will be performed at Screening, unless previously performed prior to the start of Screening (provided nothing has changed in the subject's medical history to warrant a repeat test). The MRI or high resolution CT scan of the brain for a subject who had this test done prior to Screening can be repeated at Screening as warranted based on the investigator's opinion.

The date the MRI or CT scan was performed should be available in the source documentation and will be documented in the eCRFs, including the presence or absence of tumor and type, if present. If the results of a previously performed MRI or CT scan are not available in the source documentation, the test must be repeated to establish eligibility.

Results of prior diagnostic tests used to establish eligibility should be recorded in the source documentation and entered into the appropriate eCRF.

3.25 Adrenal (All Subjects) and Testicular (Male Subjects) Ultrasound

An adrenal (all subjects) and testicular (male subjects) ultrasound will be performed at Screening unless performed prior to Screening. All ultrasounds should be performed by a trained ultrasonographer at a facility determined by the principal investigator. In addition, if the investigator has ruled out adrenal or testicular steroid secreting tumors based on previously conducted laboratory testing, the adrenal or testicular ultrasound testing to rule out such hormone secreting tumors is not required. Results of prior diagnostic tests should be recorded in source documentation and eCRF. If the results and all of the required variables listed below of a previously performed adrenal and testicular ultrasound are not available in the source documentation, the ultrasound must be repeated to establish eligibility.

[Testicular Ultrasound \(Male Subjects\)](#)

If hormone levels or testicular consistency or symmetry suggests a testicular tumor, an ultrasound of the testes, if not done previously to rule out steroid-secreting tumors, will be performed. Testes ultrasound variables to be evaluated will include volume, by measuring the length, width, and depth, and presence or absence of abnormality, and characterization (location, size) of the abnormality, if present.

[Adrenal Gland Ultrasound \(All Subjects\)](#)

An ultrasound of the adrenal gland may need to be performed if not done previously to rule out steroid-secreting tumors of the adrenal glands based on hormone levels. Adrenal ultrasound variables to be evaluated will include presence or absence of abnormality and characterization (location, size) of the abnormality, if present.

All results of prior diagnostic ultrasounds and tests used to establish eligibility should be recorded in source documentation and eCRF.

3.26 Transdermal Pelvic Ultrasound (Uterine and Ovarian Volume) (Female Subjects)

A transdermal pelvic ultrasound (to assess uterine and ovarian volume) for female subjects will be performed at Screening (unless performed prior to the start of Screening) and at other time points as specified in Section 2. A trained ultrasonographer should perform all ultrasounds (location determined by the principal investigator). Results of prior diagnostic ultrasounds and tests should be recorded in source documentation and eCRF. If the results and all of the required variables listed below of a previously performed ultrasound are not available in the source documentation, the ultrasound must be repeated to establish eligibility. The following transdermal pelvic ultrasound variables will be evaluated: ovarian and uterine volume by measuring the length, width and depth, presence of an endometrial stripe and thickness (double-layer in millimeters) if visible, presence or absence of abnormality, and characterization (including location, size) of the abnormality, if present.

3.27 Subject Withdrawal from Study

All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page; however, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment, irrespective of whether the subject or the subject's parent or legal guardian decides to continue participation in the study.

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All SAEs and study procedure-related nonserious adverse events, will be collected from the time the subject's parent or legal guardian signed the study-specific informed consent until study drug administration.

All adverse events and SAEs will be collected whether solicited or spontaneously reported by the subject and/or parent or legal guardian from the time of study drug administration through the end of the last dosing interval (24 weeks) and the 12-week Follow-up Period.

All adverse events of special interest (bone fractures/osteoporosis/osteopenia, slipped capital femoral epiphysis, neuropsychiatric events, and seizure/convulsion, injection site reaction [associated with study drug administration or stimulation test], hypersensitivity reaction) will be collected and captured. See Protocol Section 6.1, "Adverse Events of Special Interest."

4.2 Reporting Adverse Events and Intercurrent Illnesses

In the event of an SAE, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours after the site became aware of the SAE by entering the SAE data into the EDC system. SAEs that occur prior to the site's having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE nonCRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours after the site became aware of the SAE.

Email: PPDINDPharmacovigilance@abbvie.com

FAX to: +1 847-938-0660

For safety concerns, contact the Metabolic Safety Team at:

Metabolic Safety Team

Dept. R48S, Bldg. AP51-3

1 North Waukegan Road North Chicago, Illinois 60064

Office: +1 847-935-7577

Email: GPRD_SafetyManagement_Hormones@abbvie.com

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director

EMERGENCY MEDICAL CONTACT:

[REDACTED] MD

AbbVie Inc.

1 North Waukegan Road

North Chicago, IL 60064

Contact Information:

Office: [REDACTED]

Mobile: [REDACTED]

Fax: [REDACTED]

Email: [REDACTED]

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie Therapeutic Area Medical Director:

HOTLINE: +1 973-784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC.

COVID-19 Pandemic-Related Reporting

Supplemental study case report forms should be completed in the event of COVID-19 related missed/virtual visits, study drug interruptions or discontinuations, or adverse events (including capture of specific signs/symptoms of infection and testing results).

COVID-19 infections should be captured as adverse events. If the event meets the criteria for an SAE, then follow the SAE reporting directions per the protocol and above. The following COVID-19 related supplemental eCRFs should be completed:

- COVID -19 Supplemental Signs/Symptoms
- COVID-19 Status Form

If a subject has a confirmed or suspected COVID-19 infection and study drug was interrupted, the investigator should contact the sponsor emergency medical contact listed above before reintroducing study drug.

5 COUNTRY-SPECIFIC REQUIREMENTS

5.1 SUSAR REPORTING

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local guidelines, and the United States Package Insert (USPI) will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a Product Safety Update Report (PSUR) reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the "suspected" Serious Adverse Reaction will be used to assess expectedness.

5.2 Treatment After End of Study

Subjects will continue study treatment throughout the study for a period of up to 144 weeks or until premature discontinuation of study drug. At the subject's last visit, the investigator will discuss the appropriate subsequent treatment with the subject's parent or legal guardian. LA is commercially available; AbbVie will not provide LA or any other therapy once the subject's participation is concluded.

6 STUDY DRUG

6.1 Treatments Administered

Study drug (LA 45 mg 6-month) will be administered at the visits listed in Section 2. LA 45 mg 6-month drug product will be injected intramuscularly once every 24 weeks. Each injection should be administered in a different anatomical site to minimize injection site reactions.

LA 45 mg 6-month drug product will be provided by AbbVie as a pre-filled dual chamber syringe containing sterile lyophilized microspheres, which when mixed with diluent, become a suspension

intended for intramuscular injections to be given once every 24 weeks. The front chamber of the LA formulation pre-filled dual chamber syringe contains LA (45 mg), and the second chamber contains diluent. Study drug must be prepared as described in the instructions for drug preparation (refer to Section 7.3).

Study drug must not be administered without contacting the IRT system. Study drug may only be administered to subjects enrolled in the study through the IRT system. If a subject cannot come to the site because of unforeseen circumstances (e.g., the COVID-19 pandemic), the site may contact the IRT for kit assignment. Study drug can then be dispensed as described in Section 3.19.

At the end of the Treatment Period or at the Premature Discontinuation Visit, the site will contact the IRT system to provide visit date information.

The GnRHa stimulation test will be conducted using generic LA aqueous solution. For the stimulation test, 20 µg/kg of generic LA aqueous solution will be administered subcutaneously. Generic LA aqueous solution will be supplied to the sites for the purpose of conducting the stimulation test. Each site will be responsible for maintaining drug accountability records, including product description, manufacturer, lot numbers, and administration to subjects. Sites should use their standard of care practice for preparation of the injection site and injection of generic LA aqueous solution. If a subject cannot come to the site because of unforeseen circumstances (e.g., the COVID-19 pandemic), the GnRHa stimulation test may be performed by a home healthcare nurse at the subject's home.

There may be times when the sponsor is unable to provide the generic LA aqueous solution. Under these circumstances, the participating sites have the option to obtain this product through an external licensed pharmacy or wholesaler or from local site supplies.

AbbVie will not supply drug other than the study drug LA 45 mg 6-month depot formulation and the generic LA aqueous solution for the stimulation test.

6.2 Packaging and Labeling

Study drug will be supplied as open-label LA 45 mg unit dose syringes. Each kit will contain 1 pre-filled dual chamber syringe for injection.

Each kit will be labeled as required per country requirements. The label must remain affixed to the kit. The site staff will complete the blank space on the label with the subject number before administering study drug.

Storage and Disposition of Study Drug

LA 45 mg 6-month must be stored at controlled room temperature (15° to 25°C/59° to 77°F). The investigational product is for investigational use only and is to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until administered. Unused study drug should be destroyed on site as appropriate or returned to AbbVie in accordance with local regulatory requirements and AbbVie requirements.

Generic LA aqueous solution for the stimulation test should be stored per the US-approved commercial label or the clinical study label.

Temperature excursions must be reported to AbbVie immediately. Sites should use the AbbVie Temperature Excursion Management System (ATEMS) module via IRT for reporting temperature excursions for study drug (LA 45 mg 6 month), or if not accessible, fax or email copies of the Storage Temperature Excursion Reporting Form indicating the extent of the excursion (time, duration of the temperature excursion, minimum/maximum values and study drugs affected) to AbbVie Clinical Drug Supply Management (CDSM). In case of a temperature excursion, study drug should be quarantined and not administered until AbbVie CDSM or ATEMS deems the medication as acceptable. For reporting temperature excursions for generic LA aqueous solution, fax or email copies of the Storage Temperature Excursion Reporting Form to AbbVie CDSM. In case of a temperature excursion, generic LA should be quarantined and not administered until AbbVie CDSM deems the product as acceptable.

6.3 Method of Assigning Subjects to Treatment Groups

This is an open-label, nonrandomized, single-arm study. All subjects will receive the same dosage of LA (45 mg intramuscular every 24 weeks) for the duration of the study.

At the Screening Visit, all subjects will be assigned a unique subject number through the use of the IRT. For subjects who do not meet the study selection criteria, site personnel must contact the IRT system and identify the subject as a screen failure.

Subjects who are enrolled will retain their subject number assigned at the Screening Visit throughout the study. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

Contact information and user guidelines for IRT use will be provided to each site.

6.4 Selection and Timing of Dose for Each Subject

All subjects who are enrolled in the study will receive the same dose of LA (45 mg) administered intramuscularly once every 24 weeks. Study drug will be administered by site staff at scheduled study visits. If a subject cannot come to the site because of unforeseen circumstances (e.g., the COVID-19 pandemic), the study drug injection may be administered by a home healthcare nurse at the subject's home. AbbVie should be notified if this occurs.

See Section 7.3 and Section 7.4 for study drug injection preparation instructions and injection site assessment instructions, respectively.

7 Appendices

7.1 PUBERTAL STAGES WORKSHEET MALE

Subject Number: _____ Visit Date _____

Height (in triplicate) 1. _____ cm 2. _____ cm 3. _____ cm Weight _____ kg

Height Mode of Collection: Stadiometer Harpenden Other, please specify _____

	Boys' Pubic Hair	Boys' Genitalia	
Stage 1			<p><i>Testicular volume comments/observations:</i> Notes:</p> <hr/>
Stage 2			<p><i>Testicular volume comments/observations:</i> Notes:</p> <hr/>
Stage 3			<p><i>Pubic hair comments/observations:</i> Notes:</p> <hr/>
Stage 4			<p><i>Pubic hair comments/observations:</i> Notes:</p> <hr/>
Stage 5			<p><i>General comments/observations:</i> Notes:</p> <hr/>

Sources:

1. Brown RT. Adolescent growth and development. In: Holland-Hall C, Brown RT, eds. Adolescent Medicine Secrets. Philadelphia, PA: Hanley & Belfus Inc; 2002:21-8.
2. Travers SH, Slover RH. Disorders of Puberty. In: MT M, ed. Endocrine Secrets. 4th ed. Philadelphia, Pa; 2005:354-67.

7.2 PUBERTAL STAGES WORKSHEET FEMALE

Subject Number: _____ Visit Date _____

Height (in triplicate) 1. _____ cm 2. _____ cm 3. _____ cm Weight _____ kg

Height Mode of Collection: Stadiometer Harpenden Other, please specify _____

	Girls' Pubic Hair	Girls' Breasts	
Stage 1			<p>Prepubertal: No pubic hair Elevation of papilla only No palpable glandular tissue</p> <p><i>Breast development comments/observations:</i> Notes:</p> <hr/> <hr/> <hr/> <hr/>
Stage 2			<p>Sparse growth of long, straight or slightly curly, minimally pigmented hair, mainly of labia Palpable breast bud that does not extend beyond the areola; enlargement of areola</p> <p><i>Pubic hair comments/observations:</i> Notes:</p> <hr/> <hr/> <hr/> <hr/>
Stage 3			<p>Considerably darker and coarser hair spreading over mons pubis Further enlargement of breast and areola, with no separation of contours; palpable breast extends beyond the areola</p> <p><i>General comments/observations:</i> Notes:</p> <hr/> <hr/> <hr/> <hr/>
Stage 4			<p>Thick, adult-type hair that does not yet spread to medial surface of thighs Projection of areola and papilla to form secondary mound above level of breast</p> <p><i>General comments/observations:</i> Notes:</p> <hr/> <hr/> <hr/> <hr/>
Stage 5			<p>Hair adult in type and distributed in classic inverse triangle Adult contour breast with projection of papilla only</p> <p><i>General comments/observations:</i> Notes:</p> <hr/> <hr/> <hr/> <hr/>

Sources:

1. Brown RT. Adolescent growth and development. In: Holland-Hall C, Brown RT, eds. Adolescent Medicine Secrets. Philadelphia, PA: Hanley & Belfus Inc; 2002:21-8.
2. Travers SH, Slover RH. Disorders of Puberty. In: MT M, ed. Endocrine Secrets. 4th ed. Philadelphia, Pa; 2005:354-67.
3. Bonat S, Pathomvanich A, Keil MF, Field AE, Yanovski JA. Self-assessment of pubertal stage in overweight children. Pediatrics. 2002;110(4):743-7.

7.3 DOSE PREPARATION FOR LEUPROLIDE ACETATE 45 MG FORMULATION

Reconstitution and Administration for Injection of LUPRON DEPOT

- Reconstitute and administer the lyophilized microspheres as a single intramuscular injection.
- Inject the suspension immediately or discard if not used within two hours, because LUPRON DEPOT does not contain a preservative.

1. Visually inspect the LUPRON DEPOT powder. DO NOT USE the syringe if clumping or caking is evident. A thin layer of powder on the wall of the syringe is considered normal prior to mixing with the diluent. The diluent should appear clear and colorless.
2. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn (see Figure 1 and Figure 2).

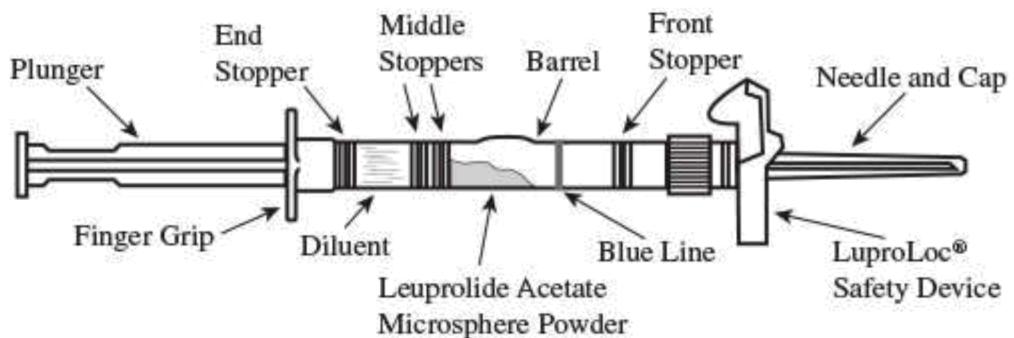


Figure 1

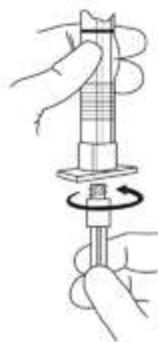


Figure 2

3. Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING (6 to 8 seconds) the plunger until the first middle stopper is at the blue line in the middle of the barrel (see Figure 3).

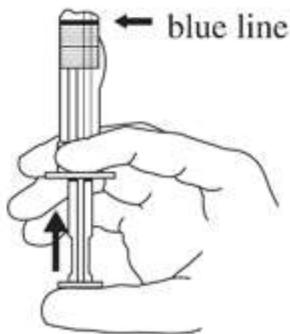


Figure 3

4. Keep the syringe UPRIGHT. Mix the microspheres (powder) thoroughly by gently shaking the syringe until the powder forms a uniform suspension. The suspension will appear milky. If the powder adheres to the stopper or caking/clumping is present, tap the syringe with your finger to disperse. DO NOT USE if any of the powder has not gone into suspension (see Figure 4).



Figure 4

5. Keep the syringe UPRIGHT. With the opposite hand pull the needle cap upward without twisting.
6. Keep the syringe UPRIGHT. Advance the plunger to expel the air from the syringe. Now the syringe is ready for injection.

7. After cleaning the injection site with an alcohol swab, administer the intramuscular injection by inserting the needle at a 90 degree angle into the gluteal area, anterior thigh, or deltoid; injection sites should be alternated (see Figure 5).

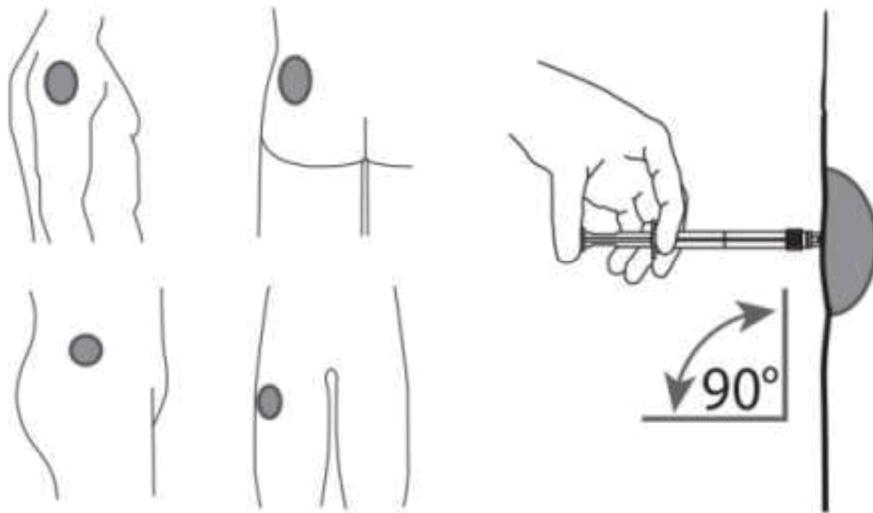


Figure 5

NOTE: If a blood vessel is accidentally penetrated, aspirated blood will be visible just below the luer lock (see Figure 6) and can be seen through the transparent LuproLoc® safety device. If blood is present, remove the needle immediately. Do not inject the medication.

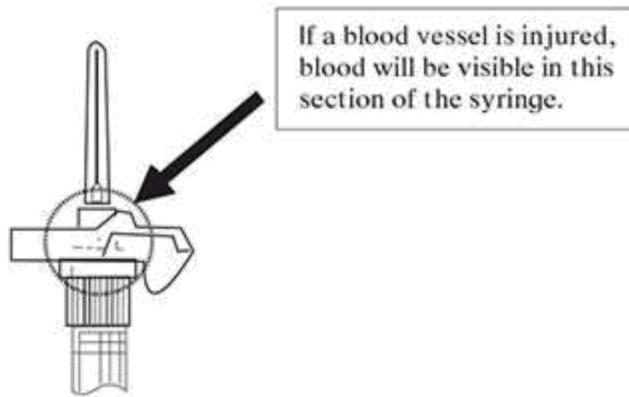


Figure 6

8. Inject the entire contents of the syringe intramuscularly.
9. Withdraw the needle. Once the syringe has been withdrawn, immediately activate the LuproLoc® safety device by pushing the arrow on the lock upward towards the needle tip with

the thumb or finger, as illustrated, until the needle cover of the safety device over the needle is fully extended and a CLICK is heard or felt (see Figure 7).



Figure 7

10. Dispose of the syringe according to local regulations/procedures.

Reference: LUPRON DEPOT Package Insert, March 2019.

7.4 LEUPROLIDE ACETATE 45 MG INJECTION SITE ASSESSMENT FORM

Subject Number: _____

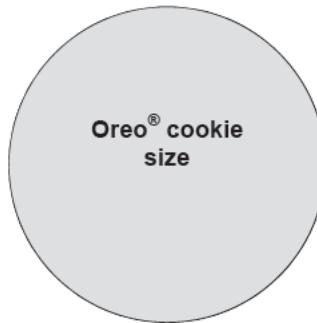
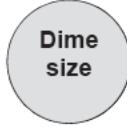
Phone Call Assessment

Date: _____

On-site Assessment

Time: _____

Home healthcare nurse assessment



18 mm

24 mm

46 mm

1. Is there any redness or swelling at the injection site? Yes No
2. If yes, estimate the largest extent of redness or swelling at the injection site in comparison to the size of the dime, quarter and Oreo cookie images provided on your Injection Site Assessment Card.

Redness: Less than a Dime Dime Quarter Oreo cookie

Swelling: Less than a Dime Dime Quarter Oreo cookie

3. Is there any drainage or abscess? Yes No
4. Does the injection site feel hot to the child? Yes No Not able to assess
5. Does the injection site feel hot to the touch by the parent? Yes No
6. Is the injection site tender or painful? If yes, rate as mild, moderate or severe

Yes Mild Moderate Severe

No

7. Does the reaction involve the whole limb? Yes No

8. Is movement of the limb limited? If yes, rate as mild or marked

Yes Mild Marked

No

9. Do the symptoms require a follow-up phone call? Yes No

10. Should the child come in to the office for an assessment? Yes No

Comments: _____

Initials of person/parent or legal guardian spoken to: _____

Signature of person completing form: _____ Date: ____ / ____ / ____

Printed name of person completing form: _____

Adapted from Skowronski, et al. "Injection-Site Reactions to Booster Doses of Acellular Pertussis Vaccine: Rate, Severity and Anticipated Impact," Pediatrics Vol. 112 No. 6, December 2003, pp.e453-459

7.5 HORMONAL FLARE AND ACUTE-ON-CHRONIC RESPONSE FORM

Phone Call Assessment

On-site Assessment

Home healthcare nurse assessment

Subject Number: _____

Date: _____

Time: _____

1. Since receiving the leuprolide acetate (45 mg) injection, is your child exhibiting any behavior that is different than their usual behavior? Yes No

If yes, please describe:

2. Is your child exhibiting any physical symptoms that are different than usual?

Yes No

If yes, please describe:

3. Do the symptoms require a follow-up phone call? Yes

No

4. Should the child come in to the office for an assessment/additional assessment?

Yes No

Comments: _____

Initials of person/parent spoken to: _____

Signature of person completing form: _____ Date: ____/____/____

Printed name of person completing form: _____

7.6 MENSTRUAL BLEEDING CALENDAR

Subject Number: _____

Date Calendar Given to Subject/Parent or Legal Guardian: _____

Instructions:

- Circle the dates when vaginal bleeding requires protection GREATER than a panty shield.
- Mark "S" on the dates when spotting occurs that DOES NOT require protection greater than a panty shield.
- Place no marks on the calendar on the dates when there's no bleeding or spotting.
- Initial this page (person who completes the calendar).

See Example Calendar Below:

November 2017						
S	M	T	W	T	F	S
			1	2	3	4
5	6	7	8 S	9 S	(10)	(11)
12 S	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

Initials and date: _____