Clinical Study Protocol

An Open-label, Single Arm, Multicenter Study on the Efficacy, Safety, and Pharmacokinetics of Leuprolide Acetate 45 mg for Injectable Suspension Controlled Release in Subjects with Central (Gonadotropin-Dependent) Precocious Puberty

NCT02452931

25 August 2015

TOLMAR Inc.

An Open-label, Single Arm, Multicenter Study on the Efficacy, Safety, and Pharmacokinetics of Leuprolide Acetate 45 mg for Injectable Suspension Controlled Release in Subjects with Central (Gonadotropin-Dependent) Precocious Puberty

Protocol Number: TOL2581A

Sponsor:

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Clinical Study Type: Pivotal: Efficacy, Safety, Pharmacokinetics

Version History:

3.0	25 August 2015
2.0	21 April 2015
1.0	28 January 2015

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CLINICAL PROTOCOL APPROVAL

SIGNATURES

[redacted]
Printed Name

Vice President, Clinical Development
Title

[redacted]
Signature

25/Aug/2015
Date

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Director, Clinical Operations
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25 Aug 2015
Date

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Medical Monitor
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25 August 2015
Date

Principal Investigator Agreement

Protocol No: TOL2581A

Protocol Title: An Open-label, Single Arm, Multicenter Study on the Efficacy, Safety, and Pharmacokinetics of Leuprolide Acetate 45 mg for Injectable Suspension Controlled Release in Subjects with Central (Gonadotropin-Dependent) Precocious Puberty

I have carefully read and understand the aforementioned Protocol and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this Protocol, International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), the Code of Federal Regulations, the Health Insurance Portability and Accountability Act (HIPAA), and local regulatory and privacy guidelines for clinical studies.

I will ensure that the rights, safety, and welfare of subjects under my care are protected. I will ensure control of the study drugs under investigation in this study. I will provide copies of the Protocol and all other study-related information supplied by TOLMAR Inc. to all personnel responsible to me who participate in the study. I will discuss this information with them to ensure that they are informed regarding the data integrity, safety of the subjects, study drug and conduct of the study. I agree to keep records on all subject information (electronic case report forms, source documents, medical records, and all other information collected during the study) and drug disposition (shipment and drug return forms) in accordance with standards set forth by the U.S. Food and Drug Administration (FDA) and local regulations applicable to clinical studies. I will not enroll any subjects into this Protocol until the applicable Independent Review Board (IRB) or Independent Ethics Committee (IEC) and Sponsor or designee approvals of the site are obtained. Only I, as the Principal Investigator, will sign the electronic Case Report Form (eCRF) and I may not designate this activity to anyone else. I will make all efforts to complete the study within the time designated.

_____

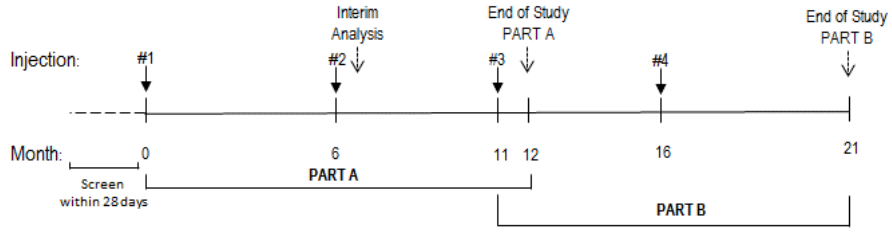
Principal Investigator Name (Print)

_____ _____

Principal Investigator Signature Date

1. SYNOPSIS

Title of Study	An Open-label, Single Arm, Multicenter Study on the Efficacy, Safety, and Pharmacokinetics of Leuprolide Acetate 45 mg for Injectable Suspension Controlled Release in Subjects with Central (Gonadotropin-Dependent) Precocious Puberty
Clinical Study Type	Adaptive Design Interventional (Efficacy, Safety and Pharmacokinetics)
Clinical Study Phase	Phase III (Pivotal)
Study Period	Total study enrollment is expected to take approximately 12 months for Part A and approximately 10 months for Part B. **Part A:** Approximately 24 months for first subject first visit (FSFV) to last subject last visit (LSLV) **Part B (Extension):** Continuation into Part B will be dependent on results from Part A. If this extension is invoked, the study will be extended for 2 more injections; therefore, FSFV to LSLV (altogether for both Parts A and B) will be approximately 34 months.
Duration of Participation	Screening Period: Up to 28 days Treatment Period, Part A: 1st and 2nd injections separated by approximately 6 months (24 weeks); subject participation is approximately 12 months Treatment Period if Part B is conducted: additional 3rd and 4th injections separated by approximately 5 months; subject participation is a total of approximately 21 months from first dose in Part A
Investigational Product (Study Drug)	Leuprolide acetate 45 mg for injectable suspension, controlled release for subcutaneous injection (ELIGARD® 45 mg, TOLMAR Inc.)
Objectives	**Primary:** • Determine the effectiveness of leuprolide acetate 45 mg for injectable suspension for treatment of children with Central Precocious Puberty (CPP). **Secondary:** • Evaluate the safety and tolerability of leuprolide acetate 45 mg for injectable suspension in children with CPP. • Characterize the burst kinetics of leuprolide acetate 45 mg after the first administration. • Characterize the pharmacodynamic (PD) relationship of leuprolide serum concentrations to concentrations of serum luteinizing hormone (LH), follicle stimulating hormone (FSH) and to testosterone/estradiol. • Assess percent changes in height velocity and bone age progression after the first administration. • Assess changes in physical signs of puberty as measured by changes in Tanner stages or in changes or onset of menses. • Determine the dosing interval (5 or 6 months) at which leuprolide acetate is able to suppress LH concentration to <4 mIU/mL (after

	gonadotropin releasing hormone agonist [GnRHa] stimulation test), as data permit.
Study Design	This will be an adaptive design study conducted in two parts as illustrated below.  *Subjects will only receive Injections #3 and #4 if Part B is conducted, based on Part A interim data.* **Part A:** This will be a multicenter, open-label, single-arm 12-month study. Pediatric subjects who have been diagnosed with CPP but have not yet received GnRH agonist therapy (drug-naïve) will be eligible (see Inclusion/Exclusion Criteria). All subjects will have a GnRHa stimulation test to confirm a diagnosis of CPP. Pediatric subjects will receive their first study drug injection at their baseline visit on Day 0 and the second injection at the Month 6 visit with periodic evaluations and monitoring for up to a total of 12 months following the first injection. Subjects will return to the clinic as indicated in the Schedule of Assessments (SoA) periodically for 12 months from start of dosing for efficacy, safety and pharmacokinetic (PK) assessments. All subjects will participate in Part A to evaluate the efficacy of leuprolide acetate injection suspension 45 mg (study drug) in suppressing LH after a GnRHa stimulation test. An independent Data Safety Monitoring Board (DSMB) will review the safety of the drug throughout the study. An interim analysis of LH suppression from the GnRHa stimulation test results will be conducted after approximately 40% of the 40 subjects anticipated to complete 6 months of assessments have data through the Month 6 visit (N = approximately 16). Based on this analysis, if LH concentrations, after the GnRHa stimulation test, are suppressed to < 4 mIU/mL in < 85% of these subjects, then Part B of the study will be invoked. All subjects still undergoing therapy in the Part A of the study and those yet to enroll in the study, if eligible, will be asked to participate in the Part B extension study for additional dosing at shorter intervals. The progression to Part B extension will be based on evaluations by the DSMB and Sponsor. **Part B Extension:** This will be a multi-center, open-label, single-arm extension following Part A. Because the interim analysis will only provide data from a very small sample size informing the decision to conduct Part B of the study with a 5-month dosing interval, **ALL** new subjects being enrolled into the study will begin with Part A of the study with the first 6-month dosing interval before proceeding to Part B. In this manner, there will be adequate data for comparison of dosing intervals for assessment of optimal efficacy. Only subjects who have received Injection #2 of study drug in Part A will be permitted to enter Part B. Injections #3 and #4 will be

	administered in 5-month intervals after Injection #2. Subjects will return to the clinic periodically up to an additional 10 months from start of Part B for efficacy and safety assessments.
Number of Study Sites	Multicenter: approximately 20 sites in the United States, Mexico, Argentina, Canada, South Korea, Australia, and New Zealand. Clinical sites in other countries may be added as necessary.
Number of Subjects	**Part A:** Approximately 60 subjects will be screened and/or enrolled in order to have approximately 40 evaluable subjects that complete 6 months of the study. **Part B Extension:** If this part is invoked, it is anticipated that approximately 27 of the enrolled subjects in Part A will participate.
Eligibility Criteria	Inclusion Criteria: 1. Females age 2 to 8 years (inclusive) or males age 2 to 9 years (inclusive) 2. Confirmed diagnosis of CPP within 12 months of Baseline Visit (Day 0) but have not received prior GnRH agonist treatment for CPP 3. Pubertal-type LH response following an abbreviated GnRHa stimulation test before treatment initiation > 5 mIU/mL 4. Clinical evidence of puberty, defined as Tanner stage ≥ 2 for breast development in females or testicular volume ≥ 4 mL in males 5. Willing and able to participate in the study 6. Difference between bone age (Greulich and Pyle method) and chronological age ≥ 1 year 7. Signed Institutional Review Board/Independent Ethics Committee (IRB/IEC)-approved informed consent form (ICF) by one or both parents (per IRB/IEC requirements), by the custodial parent or by the legal guardian(s) (if required) 8. Signed Assent by subjects as per IRB/IEC requirements Exclusion Criteria: 1. Gonadotropin-independent (peripheral) precocious puberty: extra pituitary secretion of gonadotropins or gonadotropin-independent gonadal or adrenal sex steroid secretion 2. Prior or current GnRH treatment for CPP 3. Non-progressing isolated premature thelarche 4. Presence of an unstable intracranial tumor or an intracranial tumor requiring neurosurgery or cerebral irradiation. Subjects with hamartomas not requiring surgery are eligible. 5. Any other condition, chronic illness or treatment that, in the opinion of the Investigator, may interfere with growth or other study endpoints (eg, chronic steroid use [except mild topical steroids], renal failure,

	diabetes, moderate to severe scoliosis, previously treated intracranial tumor). 6. Prior or current therapy with medroxyprogesterone acetate, growth hormone or insulin-like growth factor-1 (IGF-1) 7. Major medical or psychiatric illness that could interfere with study visits 8. Diagnosis of short stature (ie, 2.25 standard deviations (SD) below the mean height for age) 9. Positive urine pregnancy test 10. Known hypersensitivity to GnRH or related compounds 11. Any other medical condition or serious intercurrent illness that, in the opinion of the Investigator, may make it undesirable for the subject to participate in the study 12. Any other condition(s) which could significantly interfere with Protocol compliance 13. Treatment with an investigational product within 5 half-lives of that product in prior clinical studies before the baseline visit (Day 0) 14. Known history of seizures, epilepsy, and/or central nervous system disorders that may be associated with seizures or convulsions 15. Prior (within 6 months of Baseline (Day 0)) or current use of medications that, per Investigator opinion, have been associated with seizures or convulsions
Dose and Mode of Administration	**Part A:** Each subject will receive a total of 2 subcutaneous (SC) injections of leuprolide acetate 45 mg for injectable suspension (study drug) at 6-month intervals: one at Baseline (Day 0) and one at the Month 6 visit. **Part B Extension:** If invoked, eligible subjects will receive a 3rd and 4th SC injection of study drug at 5-month intervals, one at the Month 11 visit and one at the Month 16 visit.
Study Visits	**Part A:** Subjects will come to the clinic for Screening and, if eligible, for 8 subsequent study visits for up to 12 months. If Part B Extension is invoked, subjects will participate in the first 6 study visits in Part A prior to entering Part B. **Part B Extension:** Subjects will come to the clinic for 5 additional visits for up to an additional 10 months (totaling 21 months altogether for both Parts A and B).
Efficacy (Pharmacodynamic) Parameters	Blood samples will be collected during the study to measure concentrations of the following hormones: luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone/estradiol. The primary endpoint will be the percentage of subjects with serum LH concentrations < 4 mIU/mL, 30 minutes following an abbreviated GnRHa stimulation test. Other hormonal changes will provide supportive evidence of efficacy.

Pharmacokinetic Parameters	Blood samples will be collected during the study for analysis of serum leuprolide concentrations. Blood samples will be assayed and used to characterize initial burst phase and baseline or trough concentrations of leuprolide acetate following administration of the first dose of the study drug and the relationship of leuprolide to changes in serum concentrations of LH, FSH, and testosterone/estradiol.
Statistical Methods	**Data Sets to be Analyzed:** Safety population: All subjects providing consent/assent and who received at least one dose of the study drug. Intent-to-Treat (ITT) population: Subjects providing consent/assent who received at least one dose of the study drug, fulfilled the protocol eligibility criteria, and provided at least one PD laboratory assessment post dosing. Per Protocol (PP) population: Subjects who have received at least one dose of the study drug and have fulfilled the protocol in terms of eligibility, interventions and outcome assessments for at least 6 months.
	Efficacy: **Primary Efficacy Endpoint** • **Part A**: the percentage of subjects with serum LH concentrations < 4 mIU/mL 30 minutes following an abbreviated GnRHa stimulation test at the Month 6 visit • **Part B**: the percentage of subjects with serum LH concentrations < 4 mIU/mL 30 minutes following an abbreviated GnRHa stimulation test at the Month 21 visit (5 months after the Injection #4 of leuprolide acetate) **Secondary Efficacy Endpoint: Parts A & B** • The percentage of subjects with suppressed serum LH concentrations (< 4 mIU/mL) 30 minutes post GnRHa stimulation test at all assessed timepoints • Changes in height velocity (growth rate) and bone age advancement will be evaluated relative to chronological age from baseline to end of study • Change in physical signs of puberty as measure by changes in Tanner stages from baseline to end of study **Exploratory Endpoints: Parts A & B** • Bone age progression will be further evaluated using descriptive statistics and figures at all assessed timepoints. Changes in bone age progression will be described for each individual and for the ITT and PP population over the entire treatment period • Descriptive statistics will be used to describe changes in physical signs of puberty as measured by changes in Tanner stages at each assessed timepoint. Changes in Tanner staging will be described for each individual and for the ITT and PP population over the entire treatment period • The percentage of subjects with LH (< 4 mIU/mL), FSH (< 2.5 mIU/mL), estradiol (< 20 pg/mL) or testosterone (< 30 ng/dL)

	suppression to prepubertal levels and serum leuprolide levels at all assessed timepoints • Evaluation of the incidence rate of GnRH antagonist reports (see Section 8.5.1) that occurred within the 2 weeks (± 2 days) following first drug administration will be descriptively compared to the incidence rate within the 2 weeks (± 2 days) after each subsequent drug administration • Evaluation of the incidence rate of GnRH antagonist reports that occurred within 2 weeks (± 2 days) following drug administration will be descriptively compared to the incidence rate within the 2 weeks (± 2 days) prior to each scheduled visit. **Pharmacokinetics:** Leuprolide serum concentrations will be analyzed for characterization of burst and trough serum concentrations. Leuprolide concentrations will be associated with changes in LH, FSH, and testosterone/estradiol changes over time to characterize the pharmacokinetic/pharmacodynamic (PK/PD) relationship. **Safety:** Statistical analysis of safety will be descriptive only. Continuous data will be summarized in tables listing the mean, standard deviation, minimum, maximum, and number of subjects in each part of the study. Changes in GnRH antagonist reports over time will be evaluated by a comparison of reported reactions for the 2 weeks after dosing to those reported at each of the scheduled visits. Categorical data will be summarized in tables listing frequency and the percentage of subjects. All data will be listed by subject.

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2. LIST OF IN-TEXT TABLES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

3.1 Abbreviations

Term	Definition
°C	Degree Celsius
°F	Degree Fahrenheit
µg	microgram
ADL	Activities of Daily Living
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the Serum Concentration-Time Curve
CFR	Code of Federal Regulations
CPP	Central Precocious Puberty
CRO	Contract Research Organization
DSMB	Drug Safety Monitoring Board
eCRF	Electronic Case Report Form(S)
EDC	Electronic Data Capture
FDA	Food and Drug Administration (United States)
FSFV	First Subject First Visit
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
GnRH	Gonadotropin Releasing Hormone
GnRHa	Gonadotropin Releasing Hormone Agonist
HbsAg	Hepatitis B surface antigen
HCVAb	Hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITT	Intent-to-Treat
kg	Kilogram(s)
LC/MS/MS	Liquid Chromatography/Mass Spectrometry/Mass Spectrometry
LH	Luteinizing Hormone
LSLV	Last Subject Last Visit
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscle volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mIU	Milli International Units

Term	Definition
mL	Milliliter(s)
mm Hg	Millimeters of Mercury
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ng	Nanogram
OTC	Over-the-counter
PD	Pharmacodynamic
PE	Physical Examination
pg	Picogram
PHI	Private Health Information
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
SD	Standard Deviation
SoA	Schedule of Assessment
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
US	United States
WHO	World Health Organization

4. ETHICS

4.1 Independent Ethics Committee or Institutional Review Board

Institutional Review Board (IRB) or Independent Ethics Committee (IEC) will approve the Protocol, Informed Consent Form (ICF), Assent Form (if required), and all other necessary documents prior to starting the study. All Protocol Amendments must be sent to the IRB/IEC for approval prior to implementation. All sites participating in this Protocol must have IRB/IEC approval before starting any study activities. IRB/IEC approvals must be provided to the Investigators in writing.

The IRB/IEC-approved ICF and Assent Form (if required) must be signed by one or both parents (per IRB/IEC requirements), by the custodial parent or by the legal guardian(s) (when applicable). An Assent Form signed by the subject may be mandated as per the local IRB/IEC requirements.

4.2 Ethical Conduct of the Study

The study will be conducted in accordance with International Conference on Harmonisation (ICH) E6, Good Clinical Practice (GCP): Consolidated Guideline and the principles of ICH E8: General Considerations for Clinical Trials. This study will also comply with the United States (US) Code of Federal Regulations (CFR) and local regulations governing the protection of human subjects, the obligations of clinical investigators and requirements for an Investigational New Drug (IND) applications. In addition, the study will be carried out in accordance with all local laws and regulations concerning clinical studies.

4.3 Subject Information and Consent

The ICF and Assent Form (if required) used for the study must comply with the applicable local and federal laws and regulations and ICH E6 GCP: Consolidated Guideline and must be approved by the Sponsor or designee prior to review by the IRB/IEC. Any subsequent changes required by the IRB/IEC must also be approved by the Sponsor or designee. Subjects and the legal guardian(s) must be informed about all aspects of the clinical study that are necessary to make the decision to participate in the clinical study. Subjects and the parent/guardian(s) must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Documentation of the discussion, the study personnel who managed/administered the ICF, and the date of informed consent must be recorded in the source documentation. Parent/guardian(s) of subjects must give informed consent in writing and each subject must sign the Assent Form, as required. Each signed ICF and Assent (if required) will be kept on file by the Investigator for inspection at any time. A copy of the signed and dated ICF and Assent (if required) will be given to the subject.

The informed consent process must be conducted, and the form(s) must be signed, before the subject undergoes any screening or baseline procedures that are performed solely for the purpose of determining eligibility for the study, in compliance with 21 CFR Part 50.

4.4 Confidentiality of Data

Subjects will not be identified individually in any publications that result from this study. Confidential subject information, including medical records and test results, will be available

only to persons affiliated with the institution at which the subject is being treated and persons employed by, or associated with, the Sponsor, except where required by law. The Food and Drug Administration (FDA) may audit any site, which includes review of medical records of study subjects, any time following submission of the data to FDA.

5. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study will be conducted at approximately 20 sites in the US, Canada, Mexico, Argentina, Australia, New Zealand and South Korea.

Sponsor	TOLMAR Inc. 701 Centre Avenue Fort Collins, CO 80526 Phone: (970) 212-4500 Fax: (970) 449-5033
Contract Research Organization	Orphan Reach USA, LLC PO Box 423, Audubon, NJ 08106 Or QED Clinical Services Limited The Learning House Winterhill, Snowdon Drive Milton Keynes, MK6 1BP United Kingdom

6. INTRODUCTION

6.1 Background

Gonadotropin releasing hormone (GnRH)-dependent Central Precocious Puberty (CPP) is characterized by early pubertal changes accompanied by advanced bone age, accelerated growth velocity and GnRH-axis activation (Antoniazzi 2004; Kim 2013). Determining if the cause of CPP is idiopathic (genetic/undetermined) or organic (central nervous system tumor/lesion) is essential to treatment. Idiopathic CPP is more prevalent in females; whereas, in males distinguishable organic pathologies are more common (Fuqua 2013; Kaplowitz 1999). Both forms of CPP may benefit from GnRH agonist (GnRHa) therapies.

The current standard for differential diagnosis for CPP is the GnRHa stimulation test (Carretto 2014, Chi 2012). For this test, a dose of 20 µg/kg body weight of aqueous leuprolide acetate is administered; serum luteinizing hormone (LH), follicle stimulation hormone (FSH) and testosterone/estradiol are measured 30 minutes post infusion (Houk 2008; Chi 2012). Serum concentrations of LH $\geq$ 5 mIU/mL at 30 minutes are diagnostic for CPP (Houk 2008).

Supportive diagnostic criteria for CPP include a combination of clinical and physical aspects before initiating treatment (Antoniazzi 2004). These tests include determining the Tanner stage (Marshall 1969) and bone age. Bone age is determined via X-ray of the non-dominant hand, from which bone length and epiphyseal plate size are used by the Greulich and Pyle method to

determine bone age (Antoniazzi 2004, Fuqua 2013). A bone age ≥ 1.5 years of chronologic age indicates accelerated bone growth and CPP.

Leuprolide acetate is a GnRHa that inhibits pituitary gonadotropin secretion and suppresses testicular and ovarian steroidogenesis. In the original studies with leuprolide acetate in subjects with CPP, daily subcutaneous (SC) administration was shown to decrease concentrations of LH and FSH in pediatric patients (Kappy 1988). These inhibitory effects are reversible when drug therapy is discontinued. Since that time, new formulations of leuprolide acetate have been developed to allow for less frequent dosing.

Leuprolide acetate has been approved as an injection formulation (Lupron Depot-PED, Product Insert-06/2013) for treatment of CPP. This formulation can be administered as once monthly intramuscular injection at doses of 7.5 mg, 11.25 mg, or 15 mg, or as once every three months at doses of 11.25 mg or 30 mg.

Leuprolide acetate is also available as a suspension formulation for SC injection (under the brand name ELIGARD®), which is currently approved for palliative treatment of advanced prostate cancer (Product Insert-05/2014), up to a maximum dose of 45 mg administered every 6 months. The leuprolide acetate 45 mg in the study drug is in a controlled release injection solution formulation with the polymer Atrigel™ and has been used extensively in over 1 million administrations for the treatment of prostate cancer.

Each different extended formulation of leuprolide acetate has different release characteristics to optimize the GnRHa activity. For example, clinical experience with leuprolide acetate has demonstrated prolonged testosterone suppression with daily administration of as little as 1 mg, or after administration in depot formulations at intervals of one month or longer (Chrisp 1991). The pharmacokinetics of GnRH agonists, includes an initial 'flare-up' of the pituitary-gonadal axis, followed by a reduced luteinizing hormone secretion by desensitization of pituitary GnRH receptors. During the first weeks of treatment, clinical signs of puberty, such as vaginal bleeding, may occur. This is a common initial effect of drugs with leuprolide acetate. The new signs/symptoms of puberty can continue beyond the second month of treatment. In the Package Insert for Eligard under Section17 (Information for Patients), it includes information, as with other GnRH agonists, that patients may experience hot flashes (flares) after injection and in the first few weeks of treatment may also experience increased bone pain, increased difficulty in urination, and the onset or aggravation of weakness or paralysis and that these symptoms should be reported. Patients should also be told that the injection site may have transient burning/stinging, slight pain, bruising, and redness that are usually mild and reversible. Rarely allergic reactions do occur and should be reported immediately.

Benefits of leuprolide acetate for the treatment of CPP include increases to or restoration of projected adult height, and protection from the psychosocial harm associated with clinically significant early puberty (Kim 2013). Leuprolide acetate has been shown to be safe and effective during treatment periods from three months to one year at doses up to 20 mg/day in humans (Yamanaka 1985).

ELIGARD® has not been approved for use in subjects with CPP; therefore, in this study, it will be considered as an investigational product or the study drug.

6.2 Rationale

The purpose of this study is to determine the safety, efficacy and tolerability of leuprolide acetate 45 mg injections in children with CPP. Efficacy is defined as suppression of serum LH concentration to levels below 4 mIU/mL. GnRH agonists are the only products approved for use in CPP. ELIGARD® 45 mg is an injectable suspension of leuprolide acetate administered periodically (currently every 6 months) to provide controlled release characteristics, which has been shown to have a favorable safety profile in adults. The 45 mg injectable formulation of leuprolide acetate is expected to provide convenience for children with CPP by less frequent office visits and thus greater compliance for maintenance of an effective and safe dose of a well-described GnRH agonist.

An adaptive protocol design has been chosen for this study due to the remote possibility that, in children with CPP, the controlled release characteristics of the leuprolide acetate 45 mg formulation may not completely suppress LH levels after 6 months but would be able to provide adequate suppression after 5 months. Therefore, the Part A of this design will evaluate the efficacy, tolerability and safety of administration of the leuprolide acetate 45 mg after 2 administrations with a dose interval of 6 months. Since this formulation has not been administered to children, who may not metabolize the injectable formulation of leuprolide in the same manner as adults, a Part B extension is planned as a contingency in which the study drug will be administered at shorter intervals (5 months). The progression to Part B extension of the study will be based on levels of LH suppression at 6 months after the first dose, in a subset of subjects, as evaluated by the a Data Safety Monitoring Board (DSMB) and Sponsor.

7. STUDY OBJECTIVES

7.1 Primary Objective

Determine the effectiveness of leuprolide acetate 45 mg for injectable suspension for treatment of children with CPP.

7.2 Secondary Objectives

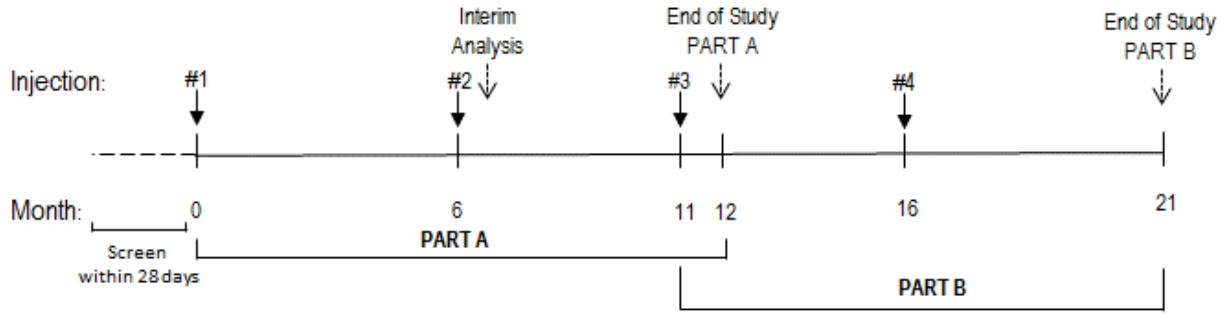
- Evaluate the safety and tolerability of leuprolide acetate 45 mg for injectable suspension in children with CPP
- Characterize the burst kinetics of leuprolide acetate 45 mg after the first administration
- Characterize the pharmacodynamic (PD) relationship of leuprolide serum concentrations to concentrations of serum LH, FSH and to testosterone/estradiol
- Assess percent changes in height velocity and bone age progression after the first administration
- Assess changes in physical signs of puberty as measured by changes in Tanner stages or in changes or onset of menses
- Determine the dosing interval (5 or 6 months) at which leuprolide acetate is able to suppress LH concentration to <4 mIU/mL (after GnRHa stimulation test), as data permit

8. INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan

This will be an adaptive design study conducted in two parts as illustrated in Figure 1.

Figure 1 Study Design



Subjects will only receive Injections #3 and #4 if Part B is conducted, based on Part A interim data.

Part A:

This will be a multi-center, open-label, single-arm 12-month study. Pediatric subjects with CPP will receive their first SC injection of the study drug (leuprolide acetate 45 mg for injectable suspension) at the start of the study and the second injection at the Month 6 visit. Subjects will return to the clinic periodically for 12 months from the start of dosing for assessment of efficacy, safety and pharmacokinetics (PK).

An independent DSMB will review the safety of the drug throughout the study.

An interim analysis of LH suppression from the GnRHa stimulation test results will be conducted after approximately 40% of the 40 subjects anticipated to complete 6 months of assessments have data through the Month 6 visit (N = approximately 16). Based on this analysis, if LH concentrations after the GnRHa stimulation test are suppressed to < 4 mIU/mL in < 85% of these subjects, then Part B of the study will be invoked. All subjects still undergoing therapy in the Part A of the study and those yet to enroll in the study, if eligible, will be asked to participate in the Part B extension study for additional dosing at shorter intervals. The progression to Part B extension will be based on evaluations by the DSMB and Sponsor.

Part B Extension:

This part of the study will be conducted based on analysis of interim data from Part A.

NOTE: Because the interim analysis will only provide data from a very small sample size informing the decision to conduct Part B of the study with a 5-month dosing interval, **ALL** new subjects being enrolled into the study will begin with Part A of the study with the first 6-month dosing interval before proceeding to Part B. In this manner, there will be adequate data for comparison of dosing intervals for assessment of optimal efficacy.

If invoked, this will be a multi-center, open-label, single-arm extension following Part A. Only subjects who have received the second injection of the study drug in Part A will be permitted to

enter Part B extension. Injections #3 and #4 will be administered in 5-month intervals after Injection #2 in Part A. The dosing interval will be dependent on emerging data from Part A. Subjects will return to the clinic periodically up to approximately an additional 10 months from start of Part B for efficacy, safety and PK assessments.

8.1.1 Duration of Study

In Part A, after a 28-day screening period, each subject will participate in the study for 48 weeks. Six months after Injection #1 in Part A, subjects will receive Injection #2 of the study drug. There will be a total of 7 study visits during Part A for a total duration of approximately 12 months.

Part A of the study is expected to take up to 24 months from first subject first visit (FSFV) to last subject last visit (LSLV), if Part B is not conducted.

After the interim analysis, if the DSMB and the Sponsor make the decision to conduct Part B of the study then all currently enrolled eligible subjects and all newly enrolled subjects will receive a total of 4 injections of the study drug. Subjects who have gone beyond the Month 11 visit will not be considered eligible to participate in Part B extension as they would be considered to be out-of-window for Injection #3.

If Part B of the study is invoked, the study length (for both Parts A and B) will be expected to be extended for approximately 10 more months for a total of approximately 34 months from FSFV (Injection #1) to LSLV. With the addition of Part B, commitment of each subject in the study will increase from 12 months to 21 months.

8.1.2 Number of Subjects

Approximately 60 pediatric subjects with CPP will be enrolled in this multicenter study so that approximately 40 subjects complete 6 months of the study.

If Part B extension of the study is invoked, it is expected that approximately 27 subjects will complete outcome assessments to the Month 21 visit (5 months after the 4^{th} study drug administration).

8.1.3 Subject Recruitment/Enrollment

Subjects will be evaluated for study inclusion only after written ICF and Assent (if required) has been obtained. Prior to enrollment during the Screening Period, each subject's inclusion/exclusion criteria information, including current and recent medications, will be reviewed to verify that the subject qualifies for the study and is not receiving any prohibited medications/treatment. After meeting all of the inclusion and none of the exclusion criteria, subjects will be eligible to enroll in the study.

8.1.4 Randomization

There is only one Investigational Product (referred to as study drug) in this study; hence, there is no randomization to study groups.

8.2 Study Population

Deviations from the inclusion or exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or subject safety.

Therefore, strict adherence to the criteria as specified is essential. Subjects whose parent/guardian(s) have provided consent along with Assent (as required) to participate in the study, but fail to meet all study eligibility criteria will be considered screen failures. Screen failure subjects are not eligible for re-screening. Retesting of laboratory safety parameters, if considered necessary by the investigator, to support the re-evaluation of a medical condition or serious intercurrent illness that, in the opinion of the Investigator, would make it undesirable for the subject to participate in the study, may be permitted upon consultation with the Medical Monitor.

8.2.1 Subject Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for participation in the study:

1. Females age 2 to 8 years (inclusive) or males age 2 to 9 years (inclusive)
2. Confirmed diagnosis of CPP within 12 months of Baseline Visit (Day 0) but have not received prior GnRH agonist treatment for CPP
3. Pubertal-type LH response following an abbreviated GnRHa stimulation test before treatment initiation > 5 mIU/mL
4. Clinical evidence of puberty, defined as Tanner stage ≥ 2 for breast development in females or testicular volume ≥ 4 mL in males
5. Willing and able to participate in the study
6. Difference between bone age (Greulich and Pyle method) and chronological age ≥ 1 year
7. Signed IRB/IEC-approved ICF by one or both parents (per IRB/IEC requirements), by the custodial parent or by the legal guardian(s) (if required)
8. Signed Assent by subjects as per IRB/IEC requirements

8.2.2 Subject Exclusion Criteria

Subjects who meet <u>any</u> of the following criteria are ineligible for participation:

1. Gonadotropin-independent (peripheral) precocious puberty: extra pituitary secretion of gonadotropins or gonadotropin-independent gonadal or adrenal sex steroid secretion
2. Prior or current GnRH treatment for CPP
3. Non-progressing isolated premature thelarche
4. Presence of an unstable intracranial tumor or an intracranial tumor requiring neurosurgery or cerebral irradiation. Subjects with hamartomas not requiring surgery are eligible.
5. Any other condition, chronic illness or treatment that, in the opinion of the Investigator, may interfere with growth or other study endpoints (eg, chronic steroid use [except mild topical steroids], renal failure, diabetes, moderate to severe scoliosis, previously treated intracranial tumor).

6. Prior or current therapy with medroxyprogesterone acetate, growth hormone or insulin-like growth factor-1 (IGF 1)
7. Major medical or psychiatric illness that could interfere with study visits
8. Diagnosis of short stature (ie, 2.25 standard deviations (SD) below the mean height for age)
9. Positive urine pregnancy test
10. Known hypersensitivity to GnRH or related compounds
11. Any other medical condition or serious intercurrent illness that, in the opinion of the Investigator, may make it undesirable for the subject to participate in the study
12. Any other condition(s) which could significantly interfere with Protocol compliance
13. Treatment with an investigational product within 5 half-lives of that product in prior clinical studies before the baseline visit (Day 0)
14. Known history of seizures, epilepsy, and/or central nervous system disorders that may be associated with seizures or convulsions
15. Prior (within 6 months of Baseline (Day 0)) or current use of medications that, per Investigator opinion, have been associated with seizures or convulsions

8.2.3 Criteria for Early Discontinuation

Subjects may be discontinued from the study for any of the following reasons:

1. Parent/guardian(s) and/or subject withdrawal of consent/assent
2. Discretion of Investigator
3. Subject becomes pregnant
4. Changes in the subject's condition that, in the judgment of the Investigator, render the subject unacceptable for further treatment with the study drug
5. Serious adverse event(s) or adverse event(s) that, in the judgment of the Investigator, render the subject unacceptable for further Treatments with the study drug
6. Subject noncompliance with Protocol scheduled visits
7. Termination of the study by the Sponsor, IRB/IEC, or other regulatory authorities
8. Subject fails suppression of LH concentration to <4 mIU/mL (after GnRHa stimulation test) at Visit 3 (~Month 3/Week 12 ± 7 days)

8.2.4 Early Discontinuation of Subjects

In the event that a subject is prematurely discontinued from the study, efforts should be made to collect all clinical and laboratory data as scheduled for End of Treatment visit (See Section 8.4.1) and the subject should be followed up for safety, as appropriate. See Section 8.5.6.2 for details on following up on AEs. In addition, the Investigator should complete and report, as thoroughly as possible, the reasons for withdrawal.

Subjects who discontinue from the study will be treated as per the Investigator's discretion and standard of care for children with CPP.

8.3 Investigational Product (Study Drug)

8.3.1 Treatments Administered

8.3.1.1 During Study Period

In Part A of the study each subject will receive a total of 2 single doses of the study drug administered as a SC injection into the abdominal area over the 12 month study period. The 2 injections of the study drug will be at 6-month intervals: one at Baseline (Day 0) and one at the Month 6 visit (24 weeks).

If Part B extension is conducted, then subjects will receive 2 additional SC administrations of the study drug at 5-month intervals: one at the Month 11 visit and one at the Month 16 visit.

8.3.2 Description of Investigational Product

The study drug, manufactured by TOLMAR, is a suspension of leuprolide acetate (ELIGARD®) for SC injection, provided in a single-use kit. The kit consists of a two-syringe mixing system, a sterile needle (18-gauge, 5/8-inch), a silicone desiccant pouch to control moisture uptake. Each syringe is individually packaged. One syringe contains the ATRIGEL® Delivery System and the other contains leuprolide acetate. When constituted, the study drug is administered as a single dose.

8.3.3 Method of Blinding

There will be no blinding of the study drug.

8.3.4 Investigational Product Storage

The Investigational Product or study drug is to be stored in a secure location. The kit should be stored refrigerated at 2°C to 8°C (36°F to 46°F).

Prior to the injection time, the two-syringe mixing system kit should be brought to room temperature at least 30 min prior to administration. The provided Pharmacy Manual contain detailed instructions on the necessary steps for mixing of the leuprolide acetate prior to administration. Once the contents of the two syringes are mixed, the final product must be administered in ≤ 30 minutes.

8.3.4.1 Administration

The specific location chosen for the study drug should be an area with sufficient soft or loose subcutaneous tissue (eg, upper- or mid-abdominal areas). Avoid areas with brawny or fibrous subcutaneous tissue or locations that could be rubbed or compressed (eg, with a belt or clothing waistband).

Topical or local anesthetic to "numb" the study drug injection site is permissible but must be recorded as a concomitant medication including the time of its administration.

8.3.4.2 Treatment Compliance

All study drug injections will be administered by study staff at the clinic. The date and time of doses administered in the clinic will be recorded in the source documents.

8.3.5 Method for Assigning Subject Numbers

A unique subject number will be assigned to each subject. Neither subject initials nor other private health information (PHI), except date of birth and sex, will be collected on study documents.

8.3.6 Investigational Product Accountability

The accounting for the receipt, administration and disposition of all investigational product/study drug by each clinical site is required. This information will consist of the date the study drug has been received at the clinical site, date administered, the subject number, and if and when investigational product/study drug was destroyed or returned. The Investigator must maintain a complete and current dispensing and inventory record in accordance with the Protocol and any applicable laws and regulations. Throughout the study, Investigational Product/study drug accountability review and reconciliation for the study drug must be maintained, and any discrepancies must be investigated and their resolution documented.

Inventory records must be readily available for inspection by the study monitor and/or auditor, and open to regulatory authority inspection at any time.

All study drug receipt, inventory, dispensing, dosing and reconciliation records will be maintained in compliance with FDA and local regulations.

8.3.6.1 Accountability and Investigational Product Use

The Investigator agrees to ensure that dispensation of the study drug occurs only at the study site(s) listed on the Form FDA 1572 (or investigator agreement/statement). The Investigator or designee also agrees that only subjects enrolled in the study may receive administration of the study drug at the clinical site. Clinical supplies may not be used for any purpose other than as stated in this Protocol.

The dispensing of all the study drug will be recorded in a dispensing log. The subject number, time of administration, and the initials and date of the person dispensing the medication will be documented on this form. The dispensing log will include the study drug identification lot numbers of the kit and both syringes.

8.3.6.2 Disposition of Used Supplies

The Investigator is responsible for accounting for all used study drug. This information will be recorded on the Drug Dispensing Log or other appropriate study drug inventory log. Used supplies should be disposed of in an appropriate manner according to institutional policy.

8.3.6.3 Inventory of Unused Supplies

The Investigator is responsible for accounting for all unused study drug. Periodically throughout and at the conclusion of the study, an inventory of unused study drug will be conducted by a representative of the Sponsor.

8.3.7 Concomitant Medications

All concomitant medications including over-the-counter (OTC) medications, herbal, botanical and nutritional supplements used during the study must be recorded in the appropriate eCRF (Concomitant Medication Form) along with the indication for which it was used. The generic name of the medications should be specified along with the dosage, frequency and duration of treatment.

Any medication considered necessary for the subject's welfare, which is not expected to interfere with the PK assessment of study drug, may be given at the discretion of the Investigator.

8.3.7.1 Permitted Medications

Medications that are used to treat acute conditions are permitted. Any medications that are used for previously identified conditions may be continued but must be recorded in the medical history and in the list of concomitant medications.

Local or topical anesthetics may be used and must be recorded as a concomitant medication with the generic name, time of administration, type and route of administration.

8.3.7.2 Prohibited Medications

Subjects shall receive no other GnRH or GnRH agonist therapy for any indication during this study. No additional hormonal therapies of any kind are permitted during this study. Subjects shall not receive any concomitant medications that, in the Investigator's opinion, have been associated with seizures or convulsions or will put the child at risk of seizures or convulsions.

8.3.7.3 Concomitant Procedures

Any diagnostic, therapeutic or surgical procedures performed during the study must be recorded in the eCRF, including the date, indication, description of the procedure(s), any clinical findings, and outcome.

8.4 Study Procedures

The by-visit schedule of study activities are provided in Table 1 and Table 2 for Part A and in Table 3 for Part B. Every attempt should be made to have each subject attend each visit as scheduled.

8.4.1 Schedule of Assessments

Table 1 Schedule of Assessments—Part A

Part A	Screening	Injection #1					Injection #2				End of Treatment [1]	Unscheduled Visit (PI discretion)
Visit Number:		Visit 1	Telephone Contact 1	Visit 2	Visit 3	Visit 4	Visit 5	Telephone Contact 2	Visit 6	Visit 7	Visit 8	
Scheduled Day/Week	Within 28 days	Baseline (Day 0)	Week 2 ± 2 days	Week 4 ± 7 days	Week 12 ± 7 days	Week 20 ± 7 days	Week 24 ± 7days	Week 26 ± 2 days	Week 36 ± 7 days	Week 44 ± 7 days	Week 48 ± 7 days	
Scheduled Month (approximate)		--		~Month 1	~Month 3	~Month 5	~Month 6		~Month 9	~Month 11	~Month 12	
Written Informed Consent / Assent [2]	X											
Inclusion/Exclusion Criteria Review	X	X										
Demographics	X											
Medical History	X											
Complete Physical Examination	X										X	X
Query Subject: How have you felt in the last 2 weeks?			X	X	X	X	X	X	X	X	X	X
Directed Physical Examination		X		X	X		X		X			
Prior or Concomitant Medication Review / Medical Procedures	X	X		X	X	X	X		X	X	X	X
Tanner Stage	X				X		X		X		X	X
Vital Signs [3]	X	X		X	X	X	X		X	X	X	X
Weight	X	X		X	X	X	X		X	X	X	X
Height	X	X		X	X	X	X		X	X	X	X
Hand and Wrist X-ray	X						X				X	

[1] If a decision is made to continue into Part B, neither Part A Visit 7 nor the End of Treatment assessment will be completed and subjects will proceed directly to the start of Part B Visit 7 of the study. See the following Schedule of Assessment for Part B.

[2] Informed Consent/Assent may be signed within 28 days prior to the Baseline visit

[3] Vital signs to be measured BEFORE any blood draws

Part A	Screening	Injection #1					Injection #2				End of Treatment [1]	Unscheduled Visit (PI discretion)
Visit Number:		Visit 1	Telephone Contact 1	Visit 2	Visit 3	Visit 4	Visit 5	Telephone Contact 2	Visit 6	Visit 7	Visit 8	
Scheduled Day/Week	Within 28 days	Baseline (Day 0)	Week 2 ± 2 days	Week 4 ± 7 days	Week 12 ± 7 days	Week 20 ± 7 days	Week 24 ± 7days	Week 26 ± 2 days	Week 36 ± 7 days	Week 44 ± 7 days	Week 48 ± 7 days	
Scheduled Month (approximate)		--		~Month 1	~Month 3	~Month 5	~Month 6		~Month 9	~Month 11	~Month 12	
Urine Pregnancy Test—females only		X					X				X	X
Urinalysis	X			X			X				X	X
Hematology	X			X			X				X	X
Chemistry	X			X			X				X	X
Hepatitis B antigen/Hepatitis C antibody	X											
Serum lipids - fasting	X	X										

Schedule of Assessments – Part A continued on next page

Table 1 Schedule of Assessments—Part A (continued)

Part A	Screening	Injection #1					Injection #2				End of Treatment [4]	Unscheduled Visit (PI discretion)
Visit Number:		Visit 1	Telephone Contact 1	Visit 2	Visit 3	Visit 4	Visit 5	Telephone Contact 2	Visit 6	Visit 7	Visit 8	
Scheduled Day/Week	Within 28 days	Baseline (Day 0)		Week 4 ± 7 days	Week 12 ± 7 days	Week 20 ± 7 days	Week 24 ± 7days		Week 36 ± 7 days	Week 44 ± 7 days	Week 48 ± 7 days	
Scheduled Month (approximate)		--		~Month 1	~Month 3	~Month 5	~Month 6		~Month 9	~Month 11	~Month 12	
LH and FSH samples (basal)	X	See Table 2		X	X	X	X		X	X	X	X

[4] If a decision is made to continue into Part B, neither Part A Visit 7 nor the End of Treatment assessment will be completed and subjects will proceed directly to the start of Part B Visit 7 of the study. See the following Schedule of Assessment for Part B.

Part A	Screening	Injection #1					Injection #2				End of Treatment [4]	Unscheduled Visit (PI discretion)
Visit Number:		Visit 1	Telephone Contact 1	Visit 2	Visit 3	Visit 4	Visit 5	Telephone Contact 2	Visit 6	Visit 7	Visit 8	
Scheduled Day/Week	Within 28 days	Baseline (Day 0)		Week 4 ± 7 days	Week 12 ± 7 days	Week 20 ± 7 days	Week 24 ± 7days		Week 36 ± 7 days	Week 44 ± 7 days	Week 48 ± 7 days	
Scheduled Month (approximate)		--		~Month 1	~Month 3	~Month 5	~Month 6		~Month 9	~Month 11	~Month 12	
Testosterone/estradiol samples (basal)	X	See Table 2		X	X	X	X		X	X	X	X
Serum Leuprolide samples (basal) [5]	X	See Table 2		X	X	X	X		X	X	X	X
GnRHa Stimulation (SC leuprolide acetate) [6]	X				X		X		X		X	X
LH and FSH samples 30 ± 5 min AFTER GnRHa stimulation	X				X		X		X		X	X
Testosterone/estradiol samples 30 ± 5 min AFTER GnRHa stimulation	X				X		X		X		X	X
Study drug (leuprolide acetate) SC injection [7]		X					X					
Adverse Events Assessment		X		X	X	X	X		X	X	X	X
Schedule/Confirm Next Visit	X	X		X	X	X	X		X	X		(X)

[5] Blood samples for leuprolide serum concentrations must be collected BEFORE the GnRHa stimulation test.
[6] GnRHa (SC) stimulation must be performed AFTER a blood sample has been collected for measurement of basal LH, FSH AND testosterone/estradiol concentrations and prior to study drug injection. Blood samples for LH, FSH and testosterone/estradiol concentrations must be obtained again 30 ± 5 minutes after SC administration of GnRHa. See Section 8.4.14.
[7] Local or topical anesthetic may be used at the discretion of the Investigator, prior to study drug administration. Name of the anesthetic used, route, and time of dose must be recorded.

Table 2 Blood Sampling Times by Parameter for Visit 1—Part A

Visit Number—Part A	Visit 1			
Scheduled Day/Month	Baseline (Day 0)			
	Time relative to injection			
	≥30 min prior	1 h (±5 min)	4 h (±10 min)	6 h (±15 min)
LH and FSH samples	X	X	X	X
Testosterone/estradiol samples	X	X	X	X
Serum Leuprolide	X	X	X	X

Vital signs to be measured BEFORE any blood draws.

Table 3 Schedule of Assessments—Part B

Part B	**Injection #3**			**Injection #4**			**End of Treatment**	**Unscheduled Visit (PI discretion)**
Visit Number:	**Visit 7**	**Telephone Contact 3**	**Visit 8**	**Visit 9**	**Telephone Contact 4**	**Visit 10**	**Visit 11**	
Scheduled Day/Week	**Week 44 ± 7 days**	**Week 46 ±2 days**	**Week 60 ± 7 days**	**Week 64 ± 7 days**	**Week 66 ±2 days**	**Week 76 ± 7 days**	**Week 80 ± 7 days**	
Scheduled Month (approximate)	**~Month 11**	**~Month 11.5**	**~Month 15**	**~Month 16**	**~Month 16.5**	**~Month 20**	**~Month 21**	
Written Informed Consent / Assent [8]	X							
Complete Physical Examination							X	X
Query Subject: How have you felt in the last 2 weeks?	X	X	X	X	X	X	X	X
Directed Physical Examination	X		X	X		X		
Prior or Concomitant Medication Review / Medical Procedures	X		X	X		X	X	X
Tanner Stage	X		X	X		X	X	X
Vital Signs [9]	X		X	X		X	X	X
Weight	X		X	X		X	X	X
Height	X		X	X		X	X	X
Hand and Wrist X-ray	X			X			X	
Urine Pregnancy Test	X			X			X	X
Urinalysis	X			X			X	X
Hematology	X			X			X	X
Chemistry	X			X			X	X
Serum lipids - fasting	X							
LH and FSH (basal)	X		X	X		X	X	X
Testosterone/Estradiol (basal)	X		X	X		X	X	X
Serum Leuprolide (basal)[10]	X		X	X		X	X	X
GnRHa Stimulation (SC leuprolide acetate)	X			X			X	X
LH and FSH samples 30 min AFTER GnRHa stimulation	X			X			X	X
Testosterone/estradiol samples 30 min AFTER GnRHa stimulation	X			X			X	X
Study drug (leuprolide acetate) SC injection [11]	X			X				
Adverse Events Assessment	X		X	X		X	X	X
Schedule/Confirm Next Visit	X		X	X		X		(X)

[8] Prior to start of Part B extension, parents/guardian(s) and subjects will be asked to sign a new ICF and assent, respectively.

[9] Vital signs to be measured BEFORE any blood draws

[10] Blood samples for leuprolide serum concentrations must be collected BEFORE the GnRHa stimulation on days the stimulation test is given.

[11] Local or topical anesthetic may be used at the discretion of the Investigator prior to study drug administration. Name of the anesthetic used, route, and time of dose must be recorded.

8.4.2 Demographic Information

Demographic and baseline characteristics, including date of birth, sex, race (American Indian; or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White), and ethnicity (Hispanic or Latino; Not Hispanic or Latino) will be collected.

8.4.3 Medical History

Relevant medical history will be collected including prior and ongoing medical illnesses, conditions, and surgical procedures within the 24 months prior to enrollment.

8.4.4 Prior and Concomitant Medications / Treatments

All prior and concomitant medications, as well as any diagnostic, therapeutic, or surgical procedures performed, will be recorded from the time of signing the ICF/Assent Form (if required) throughout the subject's participation in the study.

8.4.5 Vital Signs

Vital signs will be measured after the subject has been in a seated or supine position for 5 minutes. Vital sign assessments will include the measurement of blood pressure (mm Hg), heart rate (beats per minute), respiration rate (breaths per minute), and temperature (oral, tympanic, or temporal; °C or °F).

8.4.6 Weight

Body weight (kg) will be measured at every visit.

8.4.7 Height

Standing height will be recorded with a calibrated stadiometer (eg, "Harpenden" stadiometer) that has increments in millimeters (mm) and a functional Frankfort Plane perpendicular to the standing surface. Preferably, the same stadiometer and the same health care provider trained in the use of the stadiometer will do the repetitive measurements on any subject in the study.

The feet must be flat and either the knees or feet together in the center of the measuring board, making sure the legs are straight. The position of the legs is important. The mid-axillary line should be perpendicular to the base of the board. The subject should be looking straight ahead. In overweight, obese and older children, when the head is placed in proper position, according to the Frankfort Plane, there may be a space between the back of the child's head and the back of the measuring board. Use the Frankfort Plane on the stadiometer to determine the actual standing height to ± 1 mm.

8.4.8 Physical Examination

A complete physical exam (PE) will be performed by study personnel who are qualified to perform such examinations. At a minimum, the PE should include the cardiovascular system, the respiratory system, and the abdomen.

Thereafter, a directed or targeted PE will be performed covering body systems related to the disease, including Tanner stages, and/or to assess any ongoing AEs.

8.4.9 Tanner Stages

Sexual development in puberty will be assessed by Tanner staging, a system developed by Marshall and Tanner (1969) to categorize pubertal maturation. See Appendix 13.2 for details on the Tanner stages. Note any changes or onset of menses.

8.4.10 Clinical Laboratory Assessments

Clinical laboratory assessments (hematology, clinical chemistry, fasting serum lipids, hepatitis B & C, and urinalysis parameters) are listed in Appendix 13.1. Urinalysis assessments will be by "dipstick" assessments using urinalysis kits that will be provided to the sites by the Sponsor and evaluated locally. All other laboratory assessments will be from the blood samples collected at the appropriate assessment times and analyzed by a central laboratory.

8.4.11 Pregnancy Test

Urine pregnancy tests will be performed on female subjects. All female subjects must have a negative pregnancy test prior to receiving each injection of study drug. The pregnancy test will also be performed at End of Treatment in Part A or Part B extension (if invoked), and at the discretion of the Investigator.

8.4.12 Hand and Wrist X-Ray

A single X-ray of the non-dominant hand and wrist will be obtained periodically throughout the study to determine bone age using a Greulich and Pyle Atlas. A local reader will determine study eligibility during screening. All X-rays taken at designated study visits will be sent to a blinded central reader for evaluation of bone age; however, these evaluations will not be used to verify eligibility (eg, overrule local reader) for subject participation in the study.

8.4.13 Basal LH, FSH, Testosterone/Estradiol Concentrations

Blood samples for serum LH, FSH, testosterone (males) / estradiol (females) concentrations (as appropriate) will be collected at the appropriate assessment times and analyzed by a central laboratory according to current validated assays. It is important that ALL these samples are obtained BEFORE each study drug injection.

These samples MUST be collected BEFORE the GnRHa stimulation tests.

Blood samples will be collected and processed at the clinical site, and then shipped to the Central Laboratory for analysis according to the instructions provided in a Central Laboratory Manual.

Serum LH and FSH concentrations will be measured at the Central Laboratory using current validated chemiluminescent microparticle immunoassay with a lower sensitivity range to at least 0.5 mIU/mL (such as ARCHITECT System, Abbott Laboratory Diagnostics, USA). The lower limit of detection for testosterone/estradiol will be at least 3 ng/dL and 7.5 pg/mL, respectively. In addition, samples will be batched and analyzed by LC-MS/MS for publication purposes only.

8.4.14 Abbreviated GnRHa Stimulation Test

Baseline blood samples for serum LH, FSH, and testosterone/estradiol concentrations MUST first be obtained PRIOR to the start of the GnRHa stimulation test. A standard dose of 20 µg/kg body weight of aqueous leuprolide acetate will be administered SC. Blood samples to measure serum LH, FSH and testosterone/estradiol concentrations will be obtained again 30 minutes later.

Serum LH and FSH concentrations will be measured using current validated chemiluminescent microparticle immunoassay, as described in Section 8.4.13

8.4.15 Pharmacokinetic Assessment

All blood samples for analysis of leuprolide concentrations will be processed by a central bioanalytical laboratory. Instructions for collecting, processing, storing, and shipping blood samples will be provided in a separate PK Sample Collection, Handling and Shipping Manual.

A validated bioanalytical liquid chromatography-tandem mass spectrometry (LC/MS/MS) method will be used to measure leuprolide concentrations in serum samples.

8.5 Safety Evaluation

8.5.1 Safety Parameters

Safety parameters to be measured/assessed include eligibility assessments, medical history, vital signs, physical examinations, clinical laboratory tests, and pregnancy tests. Any abnormal hematology, serum chemistry, serum lipid, or urinalysis parameters considered clinically significant by the Investigator will be captured as AEs.

Subjects will be monitored throughout the study for AEs, as well as for changes in clinical status, vital signs, and laboratory data. Any non-serious AEs occurring from the time the ICF and Assent forms, if required, are signed until just prior to receiving the first injection of study drug will be considered as non-TEAEs unrelated to study drug administration.

Serious adverse events (SAEs) that occur as a result of study-mandated procedures during the time period after the ICF and Assent forms are signed, as appropriate, but prior to receiving the first injection of study drug will be collected but not designated as TEAEs.

In order to evaluate changes in the acute (within two weeks of administration) and chronic hormonal responses associated with GnRH antagonist treatments over time, subjects (or their parents/guardians) will be asked two weeks (14 days ± 2 days) after every study drug administration (by telephone contact), and at each scheduled visit, the following question(s):

- How have you felt in the last two weeks?

or alternatively (if the parent or guardian is answering on behalf of the subject)

- How has your child felt in the last two weeks?

Investigators will record any adverse events that are reported at that time.

In addition the investigators will categorize the more specific responses that have been identified in the table (Table 4), which are often associated with GnRH antagonist injectable treatments. If the subject (or parent/guardian) does not report any condition (within the last two weeks) that fits into the Table 4 categories, the Investigator will check the response that no conditions associated with GnRH antagonists were reported (“NO”). If any of the conditions reported by the subject (or parent/guardian) fit into one (or more) of the categories, then the Investigator will check “YES” for each applicable category. This reported information will be collected by completing Table 4:

Table 4 GnRH Antagonist Evaluations

Any GnRH antagonist conditions reported?	Yes/No
If the answer is "Yes", please categorize as described below:	
Flare or hot flashes	Yes/No
Injection site reactions *(if "Yes", please categorize below)*	Yes/No
a. burning/stinging	Yes/No
b. pain	Yes/No
c. bruising	Yes/No
d. redness	Yes/No
Difficulty in urination	Yes/No
Bone pain	Yes/No
Aggravation of weakness or other muscle symptoms	Yes/No
Onset of allergic reactions	Yes/No

All AEs should still be reported as described in Section 8.5.5. The categorization of the answers must be completed prior to any study drug administration to evaluate the chronic reports.

8.5.2 Investigator/Sponsor Safety Review

The Medical Monitor will be responsible for the ongoing evaluation of safety throughout the study. The study will be reviewed for safety on a continual basis. The Medical Monitor will have access to all laboratory data and will review all SAEs. Clinical judgment by the Medical Monitor, in consultation with the Investigator and Sponsor, will be used to determine if the study should be stopped or suspended at any time for additional review of subject safety. The Medical Monitor will make an initial determination of the expectedness of an event based on the reference safety information (Investigator Brochure and ELIGARD® Package Insert). The Medical Monitor may present summary of safety information to the DSMB.

8.5.3 Data Safety Monitoring Board

An independent DSMB will review the safety and efficacy of the drug throughout the study. The frequency of subject evaluations will be at least quarterly. The full extent of responsibilities of the DSMB will be defined in their charter.

The DSMB will review the data from the interim analysis looking at LH suppression from the GnRHa stimulation test in a subset of subjects completing the 6-month assessments to make recommendations on the progression to the Part B extension study. See Section 9.2.4 for criteria for the interim analysis data.

8.5.4 Definition of Terms

8.5.4.1 Adverse Event Definition

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (21 CFR 312.32 (a)). An AE can, therefore, be any unfavorable and unintended sign (eg, an abnormal laboratory finding considered clinically significant by the Investigator), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. For this protocol, any unfavorable and unintended sign, symptom, or disease occurring after signature of Informed Consent/Assent will be collected as AEs.

8.5.4.2 Suspected Adverse Reaction Definition

A suspected adverse reaction is defined as any AE for which there is reasonable possibility that the drug caused the AE (21 CFR 312.32 (a)).

8.5.4.3 Unexpected Adverse Event Definition

An AE or suspected adverse reaction is considered unexpected if it is not listed in the ELIGARD® Package Insert, or is not listed in the Investigator Brochure.

8.5.4.4 Serious Adverse Event Definition

An SAE is defined as any untoward medical occurrence at any dose of study drug that results in any of the following outcomes (see FDA 21 CFR 312.32 and/or ICH E6 for Good Clinical Practice: Glossary of Terms):

- Death
- A life-threatening adverse event

  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions)
- A congenital anomaly/birth defect

The following events should also be considered as serious:

- Important medical events: Events that are not immediately life threatening or do not result in death or hospitalization, but they do require urgent and intensive intervention to prevent one of the other outcomes listed in the definition above (eg, intensive treatment at home or in an emergency room for bronchospasm or seizure and a persistent high fever with temperatures over 101°F [38°C]).

8.5.5 Reporting of Adverse Events

All AEs that are observed by the Investigator or one of his/her medical collaborators, or reported by the subject, will be reported even if they are potentially attributable to unrelated medical

conditions or other medications the subject may be taking. The information recorded for AEs will include start date, a description of the AE, severity, causal relationship to Investigational Product/study drug, action taken, outcome of the event (including any treatment and/or hospitalization), and stop date. In addition, start time will be collected for events beginning on the day of the first injection.

Medical conditions or diseases present before a subject is enrolled in the study are only considered AEs if they worsen after the subject is enrolled.

For each AE, the seriousness, severity, and causal relationship to study drug will be assessed and entered in the source document. All items on the AE page of the eCRF should be completed for each AE.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the study period. Planned surgical measures and the conditions leading to these measures are not AEs, if the condition(s) was (were) known before the study treatment. In the latter case, the condition should be reported as medical history.

8.5.5.1 Severity of Adverse Events

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading scale uses Grades 1 through 5 to provide unique clinical descriptions of severity for AEs. Each AE will be rated according to NCI-CTCAE (version will be specified in the statistical analysis plan [SAP]) severity grading scale as outlined in Table 5. A complete description of each grade of the NCI-CTCAE rating system can be found on the NCI website (NCI-CTCAE version 4.0, 2010).

Table 5 National Cancer Institute Common Toxicity Criteria for Adverse Events Severity Grading Scale

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a].
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b].
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

ADL: Activities of Daily Living

a. Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Source: NCI-CTCAE version 4.0, 2010

An AE that is assessed as severe should not be confused with an SAE. An event is defined as ‘serious’ when it meets one of the pre-defined outcomes as described in Section 8.5.4.4.

8.5.5.2 Criteria for Determining Relationship of Adverse Events to Investigational Product

All AEs must be rated for their causal relationship to study drug according to the categories outlined in Table 6.

Table 6 Criteria for Determining Relationship of Adverse Event to Investigational Product

Adverse Event Relationship	Definition	Criteria
Not Related	This category applies to those AEs that the Investigator, after careful consideration, believes are clearly due to extraneous causes (disease, environment, etc) and are not related to the administered investigational product.	An adverse experience may be considered not related if, for example, the following apply: • It does not follow a reasonable temporal sequence from administration of Investigational Product • It could readily have been produced by the subject's clinical state, environment or toxic factors, or other modes of therapy administered to the subject • It does not follow a known pattern of response to Investigational Product
Related	This category applies to those AEs that the Investigator believes are related to the administrated Investigational Product.	An AE may be assigned as related if, for example, the following apply: • It follows a reasonable temporal sequence from administration of Investigational Product. • It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. • It disappears or decreases on cessation or reduction in dose of study drug and recurs with re-exposure. – **NOTE**: This is not to be construed as requiring re-exposure of the subject. • It follows a known pattern of response to the Investigational Product.

8.5.6 Serious Adverse Events

All SAEs occurring after administration of study drug and within 6 months following last dose of study drug must be reported to the representatives of TOLMAR within 24 hours after the Investigator or site personnel have been informed or first becoming aware of the event. All events that meet the definition of an SAE or suspected unexpected serious adverse reactions (SUSAR) that occur as a result of study mandated procedures during the time period after the subject signs the ICF but prior to receiving the first infusion of study drug must also be reported.

8.5.6.1 Reporting of Serious Adverse Events

When an SAE or SUSAR occurs, the Investigator or designee must log into the electronic data capture (EDC) system and complete the SAE Report form within 24 hours of first becoming aware of the SAE. All SAEs (including deaths of any cause) that occur after administration of study drug and within 6 months after the last administration of study drug in Part A, or within 5 months after the last administration of study drug in Part B is invoked, whether or not considered related to study drug must be reported. The Investigator must also report SAEs to the Sponsor or representative (contract research organization [CRO]) and to the IRB/IEC as required by local and national laws. The Investigator must maintain documentation of all communications to and from the IRB/IEC. The SAE Report from the site should include date and time of onset, description of event, severity, duration, outcome, etiology, relationship to study drug, action taken and other relevant details as available. The Investigator is also responsible for updating the SAE Report Form as additional information becomes available. The Investigator may be requested for additional follow-up information by the Sponsor or the pharmacovigilance service provider in order to have more complete information for regulatory reporting.

All SAEs/SUSARS will be monitored by the CRO Medical Monitor or pharmacovigilance service provider prior to submission to the regulatory authorities. Events associated with this clinical trial will be recorded in the ELIGARD® global safety database that is maintained for reporting and analysis.

The Sponsor will adhere to all AE regulatory reporting requirements in accordance with local regulation and local authorities.

Additional safety instructions will be provided to clinical sites including contact numbers and schedules to report all AEs, SAEs and SUSARs associated with this study.

8.5.6.2 Follow Up of Adverse Events by Investigator

After the initial SAE report, the Investigator is required to proactively follow each subject and provide further information to CRO on the subject's condition. Any AEs related to study drug will be followed for 28 days or through resolution, stabilization, until deemed clinically insignificant, or until the subject is lost to follow-up. For SAEs, follow-up is required on an expedited timeline, within 24 hours of the initial report, as described in Section 8.5.6.1.

New or updated information will be recorded in the "SAE" eCRF. The medical monitor and TOLMAR will be notified of the SAE within 24 hours as per the CRO's established processes (Section 8.5.6.1).

8.5.7 Pregnancies

If a subject becomes pregnant at any time after the first injection, she must NOT receive the subsequent injections.

Pregnancies are not considered to be AEs or SAEs; however, pregnancies will be followed through to outcome. If a pregnancy occurs, the Investigator or designee must complete the Pregnancy Report form within 24 hours of first becoming aware of the pregnancy. In pregnancies that progress to term, any congenital abnormalities in the offspring of a subject who received study drug should be reported as an SAE.

8.6 Study Visits

Each subject is considered to be enrolled in the study when the subject's parent/guardian has signed the ICF along with the subject's signed Assent (as per IRB/IEC requirement) and has been assigned a subject number. A subject is considered to have discontinued from the study after the subject and parent/guardian have withdrawn consent/assent or has been discontinued under the conditions specified in Section 8.2.3.

The following sections (Sections 8.6.1 to 8.6.199) outline the procedures required at each visit.

8.6.1 Screening Visit

Screening assessments will be performed during the 28-day Screening period and prior to the first injection, unless otherwise specified. During screening, the following procedures and evaluations will be performed:

1. Informed consent and assent (if required); may be signed up to 28 days prior to Baseline/Day 0
2. Inclusion/exclusion criteria
3. Demographics
4. Medical History
5. Vital signs – measured prior to any blood draws
6. Prior and concomitant medications
7. Physical Examination-complete
8. Tanner stage
9. Height and weight
10. X-ray of non-dominant hand and wrist
11. Urine for urinalysis, performed using dipstick supplied by Sponsor
    NOTE: results must be evaluated before dosing
12. Blood samples for clinical laboratory assessments
    - Hematology and chemistry parameters as per Appendix 13.1
    - Serum lipids, fasting for ≥8 hours (water permitted)
    - Hepatitis B Surface Antigen (HBsAg) and hepatitis C antibody (HCBAb)
13. Blood samples for basal LH, FSH, testosterone/estradiol concentrations PRIOR to the GnRHa stimulation
14. Blood samples for basal leuprolide concentrations PRIOR to the GnRHa stimulation
15. GnRHa stimulation: aqueous leuprolide acetate 20 µg/kg body weight administered SC
16. Blood samples for LH, FSH, testosterone/estradiol concentrations 30 ± 5 minutes AFTER the GnRHa stimulation
17. Schedule/confirm next visit

8.6.2 Part A, Visit 1 (Baseline, Day 0)—Injection #1

Day 0 Predose:

1. Evaluate hematology, chemistry and urinalysis results from Screening Visit
2. Inclusion/exclusion criteria – review to verify that subject continues to meet all of the inclusion and none of the exclusion criteria.
3. Physical Examination-directed

4. Prior and concomitant medications
5. Vital signs – measured prior to any blood draws
6. Height and weight
7. Urine pregnancy test, females only
   NOTE: Results must be negative prior to receiving study drug injection
8. Serum lipids, fasting for ≥8 hours (water permitted)
9. Blood samples for basal LH, FSH, testosterone/estradiol concentrations ≥30 minutes before planned injection time
10. Predose blood sample for serum leuprolide concentrations ≥30 minutes before planned injection time
11. Record all non-treatment emergent AEs from the time of informed consent/assent until first study drug administration

Day 0 Study Drug administration:

12. Pharmacy - prepare study drug for injection (see Pharmacy Manual for complete instructions)
    a. Remove kit from refrigerator at least 30 minutes prior to planned administration and allow the study drug to reach room temperature
    b. Start mixing process with the product kit within ≤ 30 minutes prior to the injection time.
13. Apply topical or local anesthetic (per Investigator discretion) to injection site prior to planned injection time; record medication, dose, route, and time
14. Administer first injection of study drug

Day 0 Postdose:

15. Blood sample for LH, FSH, testosterone/estradiol, and serum leuprolide concentrations post study drug injection time:
    a. 1 hour ± 5 minutes
    b. 4 hours ± 10 minutes
    c. 6 hours ± 15 minutes
16. Final AE assessment prior to subject discharge from clinic
17. Schedule/confirm next visit

8.6.3 Telephone Contact 1(14 days ± 2 days):

1. Query subject or parent: "How have you felt in the last two weeks?" or "How has your child felt in the last two weeks?" Complete Table 4

8.6.4 Part A, Visit 2 (~Month 1/Week 4 ± 7 days)

1. Query subject or parent: "How have you felt in the last two weeks?" or "How has your child felt in the last two weeks?" Complete Table 4
2. Vital signs - measured prior to any blood draws
3. Physical Examination—directed
4. AE and concomitant medications assessments
5. Height and weight
6. Clinical laboratory assessments (hematology, chemistry) as per Appendix 13.1
7. Urine for urinalysis, performed using dipstick supplied by Sponsor

8. Blood samples for basal LH, FSH, testosterone/estradiol concentrations
9. Blood sample for basal serum leuprolide concentrations
10. Schedule/confirm next visit

8.6.5 Part A, Visit 3 (~Month 3/Week 12 ± 7 days)

1. Query subject or parent: "How have you felt in the last two weeks?" or "How has your child felt in the last two weeks?" Complete Table 4
2. Vital signs - measured prior to any blood draws
3. AE and concomitant medications assessments
4. Physical Examination—directed
5. Tanner stage
6. Height and weight
7. Blood samples for basal LH, FSH, testosterone/estradiol concentrations PRIOR to the GnRHa stimulation
8. Blood sample for basal serum leuprolide concentrations PRIOR to the GnRHa stimulation
9. GnRHa stimulation: aqueous leuprolide acetate 20 µg/kg body weight administered SC
10. Blood samples for LH, FSH, testosterone/estradiol concentrations 30 ± 5 minutes AFTER the GnRHa stimulation
11. Schedule/confirm next visit
    NOTE: Subjects who do not show adequate suppression of LH concentration to <4 mIU/mL (after GnRHa stimulation test) will be discontinued.

8.6.6 Part A, Visit 4 (~Month 5/Week 20 ± 7 days)

1. Query subject or parent: "How have you felt in the last two weeks?" or "How has your child felt in the last two weeks?" Complete Table 4
2. Vital signs
3. Height and weight
4. AE and concomitant medications assessments
5. Blood samples for basal LH, FSH, testosterone/estradiol concentrations
6. Blood sample for basal serum leuprolide concentrations
7. Schedule/confirm next visit

8.6.7 Part A, Visit 5 (~Month 6/Week 24 ± 7 days)—Injection #2

Predose:

1. Query subject or parent: "How have you felt in the last two weeks?" or "How has your child felt in the last two weeks?" Complete Table 4
2. Vital signs - measured prior to any blood draws
3. AE and concomitant medications assessments
4. Physical Examination—directed
5. Tanner stage
6. Height and weight
7. X-ray of non-dominant hand and wrist
8. Clinical laboratory assessments (hematology, chemistry) as per Appendix 13.1
9. Urine for urinalysis, performed using dipstick supplied by Sponsor

10. Urine pregnancy test, females only
    NOTE: Results must be negative prior to receiving Injection #2
11. Blood samples for basal LH, FSH, testosterone/estradiol concentrations PRIOR to the GnRHa stimulation
12. Blood sample for basal serum leuprolide concentrations PRIOR to the GnRHa stimulation
13. GnRHa stimulation: aqueous leuprolide acetate 20 µg/kg body weight administered SC
14. Blood samples for LH, FSH, testosterone/estradiol concentrations 30 ± 5 minutes AFTER the GnRHa stimulation

Study Drug Administration:

15. Pharmacy - prepare study drug for injection (see Pharmacy Manual for complete instructions)
    a. Remove kit from refrigerator, at least 30 minutes prior to planned administration and allow the study drug to reach room temperature
    b. Start mixing process with the product kit within ≤ 30 minutes prior to the injection time.
16. Apply topical or local anesthetic (per Investigator discretion) to injection site prior to planned injection time; record medication, dose, route, and time
17. Administer second injection of study drug

Postdose:

18. Final AE assessment prior to subject discharge from clinic
19. Schedule/confirm next visit

8.6.8 Telephone Contact 2 (14 days ± 2 days) Post Injection #2

1. Query Subject or parent: "How have you felt in the last two weeks?" or "How has your child felt in the last two weeks?" Complete Table 4

8.6.9 Part A, Visit 6 (~Month 9/Week 36 ± 7 days)

1. Query subject or parent "How have you felt in the last two weeks?" or "How has your child felt in the last two weeks?" Complete Table 4
2. Vital signs - measured prior to any blood draws
3. AE and concomitant medications assessments
4. Physical Examination—directed
5. Tanner stage
6. Height and weight
7. Blood samples for basal LH, FSH, testosterone/estradiol concentrations PRIOR to the GnRHa stimulation test
8. Blood sample for basal serum leuprolide concentrations PRIOR to the GnRHa stimulation test
9. GnRHa stimulation: aqueous leuprolide acetate 20 µg/kg body weight administered SC
10. Blood samples for LH, FSH, testosterone/estradiol concentrations 30 ± 5 minutes AFTER the GnRHa stimulation test
11. Schedule/confirm next visit

8.6.10 Part A, Visit 7 (~Month 11/Week 44 ± 7 days)

NOTE: DO NOT complete Part A, Visit 7, if a decision has been made to conduct Part B extension study. In this case, follow procedures for Part B (Visits 7 to 13) beginning in Section 8.6.12.

1. Query subject or parent: "How have you felt in the last two weeks?" or "How has your child felt in the last two weeks?" Complete Table 4
2. Vital signs - measured prior to any blood draws
3. Height and weight
4. AE and concomitant medications assessments
5. Blood samples for basal LH, FSH, testosterone/estradiol concentrations
6. Blood sample for basal serum leuprolide concentrations
7. Schedule/confirm next visit

8.6.11 Part A, Visit 8 (~Month 12/Week 48 ± 7 days) End of Treatment or Early Discontinuation

1. Query subject or parent "How have you felt in the last two weeks?" or "How has your child felt in the last two weeks?" Complete Table 4
2. Vital signs – measured prior to any blood draws
3. AE and concomitant medications
4. Physical Examination-complete
5. Tanner stage
6. Height and weight
7. X-ray of non-dominant hand and wrist
8. Urine pregnancy test, females only
9. Clinical laboratory assessments (hematology, chemistry) as per Appendix 13.1
10. Urine for urinalysis, performed using dipstick supplied by Sponsor
11. Blood samples for basal LH, FSH, testosterone/estradiol concentrations PRIOR to the GnRHa stimulation test
12. Blood sample for serum leuprolide concentrations PRIOR to the GnRHa stimulation test
13. GnRHa stimulation: aqueous leuprolide acetate 20 µg/kg body weight administered SC
14. Blood samples for LH, FSH, testosterone/estradiol concentrations 30 ± 5 minutes AFTER the GnRHa stimulation test

8.6.12 Part B, Visit 7 (~Month 11/Week 44 ± 7 days)—Injection #3

The decision to conduct Part B extension of the study will be based on the results of the interim analysis (see Section 9.2.4).

Predose:

1. Informed consent and assent (may be signed up to 28 days prior to Part B, Visit 7)
2. Query subject or parent "How have you felt in the last two weeks?" or "How has your child felt in the last two weeks?" Complete Table 4
3. Vital signs - measured prior to any blood draws
4. AE and concomitant medications assessments
5. Physical Examination—directed

6. Tanner stage
7. Height and weight
8. X-ray of non-dominant hand and wrist
9. Clinical laboratory assessments (hematology, chemistry)
    a. Hematology and chemistry parameters as per Appendix 13.1
    b. Serum lipids, fasting for ≥8 hours (water permitted)
10. Urine for urinalysis, performed using dipstick supplied by Sponsor
11. Urine pregnancy test, females only
    NOTE: Results must be negative prior to receiving Injection #3)
12. Blood samples for basal LH, FSH, testosterone/estradiol concentrations PRIOR to the GnRHa stimulation
13. Blood sample for basal serum leuprolide concentrations PRIOR to the GnRHa stimulation
14. GnRHa stimulation: aqueous leuprolide acetate 20 µg/kg body weight administered SC
15. Blood samples for LH, FSH, testosterone/estradiol concentrations 30 ± 5 minutes AFTER the GnRHa stimulation test

Study Drug Administration:

16. Pharmacy - prepare study drug for injection (see Pharmacy Manual for complete instructions)
    a. Remove kit from refrigerator, at least 30 minutes prior to planned administration and allow the study drug to reach room temperature
    b. Start mixing process with the product kit within ≤ 30 minutes prior to the injection time.
17. Apply topical or local anesthetic (per Investigator discretion) to injection site prior to planned injection time; record medication, dose, route, and time
18. Administer third injection of study drug

Postdose:

1. Final AE assessment prior to subject discharge from clinic
2. Schedule/confirm next visit

8.6.13 Telephone Contact 3 (14 days ± 2 days) Post Injection #3

1. Query subject or parent "How have you felt in the last two weeks?" or "How has your child felt in the last two weeks?" Complete Table 4

8.6.14 Part B, Visit 8 (~Month 15/Week 60 ± 7 days)

1. Query subject or parent "How have you felt in the last two weeks?" or "How has your child felt in the last two weeks?" Complete Table 4
2. Vital signs - measured prior to any blood draws
3. AE and concomitant medications assessments
4. Physical Examination—directed
5. Tanner stage
6. Height and weight
7. Blood samples for basal LH, FSH, testosterone/estradiol concentrations
8. Blood sample for basal serum leuprolide concentrations
9. Schedule/confirm next visit

8.6.15 Part B, Visit 9 (~Month 16/Week 64 ± 7 days)—Injection #4

Predose:

1. Query subject or parent "How have you felt in the last two weeks?" or "How has your child felt in the last two weeks?" Complete Table 4
2. Vital signs - measured prior to any blood draws
3. AE and concomitant medications assessments
4. Physical Examination—directed
5. Tanner stage
6. Height and weight
7. X-ray of non-dominant hand and wrist
8. Clinical laboratory assessments (hematology, chemistry) as per Appendix 13.1
9. Urine for urinalysis, performed using dipstick supplied by Sponsor
10. Urine pregnancy test, females only
    NOTE: Results must be negative prior to receiving Injection #4)
11. Blood samples for basal LH, FSH, testosterone/estradiol concentrations PRIOR to the GnRHa stimulation
12. Blood sample for basal serum leuprolide concentrations PRIOR to the GnRHa stimulation
13. GnRHa stimulation: aqueous leuprolide acetate 20 µg/kg body weight administered SC
14. Blood samples for LH, FSH, testosterone/estradiol concentrations 30 ± 5 minutes AFTER the GnRHa stimulation test

Study Drug Administration:

15. Pharmacy - prepare study drug for injection (see Pharmacy Manual for complete instructions)
    a. Remove kit from refrigerator, at least 30 minutes prior to planned administration and allow the study drug to reach room temperature
    b. Start mixing process with the product kit within ≤ 30 minutes prior to the injection time.
16. Apply topical or local anesthetic (per Investigator discretion) to injection site prior to planned injection time; record medication, dose, route, and time
17. Administer third injection of study drug

Postdose:

18. Final AE assessment prior to subject discharge from clinic
19. Schedule/confirm next visit

8.6.16 Telephone Contact 4 (14 days ± 2 days) Post Injection #4

1. Query subject or parent "How have you felt in the last two weeks?" or "How has your child felt in the last two weeks?" Complete Table 4

8.6.17 Part B, Visit 10 (~Month 20/Week 76 ± 7 days)

1. Query subject or parent "How have you felt in the last two weeks?" or "How has your child felt in the last two weeks?" Complete Table 4
2. Vital signs - measured prior to any blood draws

3. AE and concomitant medications assessments
4. Physical Examination—directed
5. Tanner stage
6. Height and weight
7. Blood samples for basal LH, FSH, testosterone/estradiol concentrations
8. Blood sample for basal serum leuprolide concentrations
9. Schedule/confirm next visit

8.6.18 Part B, Visit 11 (~Month 21/Week 80 ± 7 days)—End of Treatment or Early Discontinuation

1. Query subject or parent "How have you felt in the last two weeks?" or "How has your child felt in the last two weeks?" Complete Table 4
2. Vital signs - measured prior to any blood draws
3. AE and concomitant medications assessments
4. Physical Examination—complete
5. Tanner stage
6. Height and weight
7. X-ray of non-dominant hand and wrist
8. Urine pregnancy test, females only
9. Clinical laboratory assessments (hematology, chemistry) as per Appendix 13.1
10. Urine for urinalysis, performed using dipstick supplied by Sponsor
11. Blood samples for basal LH, FSH, testosterone/estradiol concentrations PRIOR to the GnRHa stimulation
12. Blood sample for basal serum leuprolide concentrations PRIOR to the GnRHa stimulation
13. GnRHa stimulation: aqueous leuprolide acetate 20 µg/kg body weight administered SC
14. Blood samples for LH, FSH, testosterone/estradiol concentrations 30 ± 5 minutes AFTER the GnRHa stimulation test

8.6.19 Unscheduled Visits

If additional visits are needed, either during Part A or Part B, the following procedures and evaluations may be performed as deemed appropriate by the Investigator. If the subject is expected to return for subsequent visits the GnRHa stimulation test will be optional, while blood samples for hormones must be collected:

1. Query subject or parent "How have you felt in the last two weeks?" or "How has your child felt in the last two weeks?" Complete Table 4
2. Vital signs - measured prior to any blood draws
3. AE and concomitant medications assessments
4. Physical Examination—complete
5. Tanner stage
6. Height and weight
7. Urine pregnancy test, females only
8. Clinical laboratory assessments (hematology, chemistry) as per Appendix 13.1
9. Urine for urinalysis, performed using dipstick supplied by Sponsor
10. Blood samples for basal LH, FSH, testosterone/estradiol concentrations PRIOR to the optional GnRHa stimulation test

11. Blood sample for basal serum leuprolide concentrations PRIOR to the optional GnRHa stimulation test
12. At investigator's discretion: GnRHa stimulation: aqueous leuprolide acetate 20 µg/kg body weight administered SC
13. If GnRH stimulation is performed, blood samples for LH, FSH, testosterone/estradiol concentrations will be collected 30 ± 5 minutes AFTER the GnRHa stimulation
14. Schedule/confirm next visit, if appropriate

8.6.20 Study Termination

The clinical study may be stopped at any time at the discretion of the Sponsor or by regulatory authorities (IRB/IEC or governing competent authority). The clinical study may be stopped if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable.

Further recruitment in the study or at a particular site(s) may be stopped due to insufficient compliance with the Protocol, ICH-GCP and/or other applicable regulatory requirements, procedure-related problems, or if the number of discontinuations for administrative reasons is too high.

Upon study termination, all site closure activities with the investigator or site staff, as appropriate, will be conducted in accordance with applicable regulations including ICH-GCP and sponsor procedures.

After the completion of the study subjects will be managed for their underlying disease according to the local standard of care, and based on the subject's previous medical history. Continued treatment will not be conducted as part of this protocol.

9. STATISTICAL PLAN

Prior to the database lock, a finalized Statistical Analysis Plan (SAP) will be completed and approved. The SAP will contain a comprehensive explanation of the methodology used in the statistical analyses. The SAP will also contain the rules and data handling conventions that will be used to perform the analyses, and the procedure that will be used to account for missing data.

9.1 Sample Size Determination

To determine the percentage of subjects with suppression of serum LH to < 4 mIU/mL following treatment with leuprolide acetate 45 mg, it is estimated that approximately 40 subjects would be sufficient for assessment of Part A and approximately 27 subjects for Part B, if invoked. Approximately 60 subjects may be enrolled in the study in order to get an appropriate number of assessable subjects.

The sample size was pragmatically determined based on the clinical trial size and response rate of other GnRH antagonists studies in CPP subjects.

The descriptive finding that will conclude efficacy is that ≥ 80% of subjects will exhibit < 4 mIU/mL LH suppression. This is conservative, since the dropout rate is unknown, and it is anticipated that the percent of subjects suppressed is likely to be at least 85%. Thus, 85% suppression or 90% suppression might be reasonably expected. However, the drop out in this

study could be slightly more than 50%, if Part B is invoked, thus depending on whether only Part A is carried out or Part B is invoked, the final available sample size after drop out could vary between 25 and 50 subjects given the planned recruitment of 60 subjects. Suppression to < 4 mIU/mL in approximately 70% of the subjects is considered to be clinically important if the full expectations of all drop-out are completed. Thus, the study is thought to have a sufficient number of subjects. If 85% of subjects enrolled are found to be suppressed we would expect a lower 95% one sided confidence interval under a fully realized drop out scenario (ie, 25 final subjects) of slightly more that 70%.

9.2 Statistical Methods

The purpose of this study is to demonstrate suppression of LH at a level of < 4 mIU/mL at 30 minutes after GnRHa stimulation in a majority of subjects (≥ 80%) who are treated with leuprolide acetate 45 mg in an injectable suspension. Descriptive outcomes for the primary and secondary efficacy variables will be used to evaluate the efficacy of this treatment.

If suppression in ≥ 85% of the first 16 subjects to be evaluated at Month 6 is found, the study will terminate under Part A without the invocation of Part B as a follow-on adaptive dosing schedule. If study termination under Part A occurs, the criterion variable for adaptive change applied to the first 16 patients at six months, namely, percent of patients with < 4 mIU/mL suppression, will *also* function as the primary outcome variable when applied to all patients in the study. As was the case for evaluating adaptive change in design, an absolute descriptive rather than inferential statistical outcome will be used to assess efficacy for the primary outcome variable. Efficacy will be claimed if ≥ 80% of the subjects exhibit < 4 mIU/mL suppression.

If suppression in < 85% of the first 16 subjects to be evaluated at Month 6 is found, the study will be adapted and Part B will be invoked. As would be the case if the study were to terminate with Part A, the percent of subjects with < 4 mIU/mL suppression will serve as the primary outcome variable under Part B. If < 4 mIU/mL suppression in ≥ 80% of the patients in the study at Visit 11 (Month 21) is found, efficacy will be claimed.

9.2.1 Demographics and Other Baseline Characteristics

Demographic variables will include age, race, ethnicity, sex, height, and weight. Subject demographics will be summarized with descriptive statistics, as appropriate.

9.2.2 Efficacy Evaluations

Primary Efficacy Endpoint

- **Part A**: the percentage of subjects with serum LH concentrations < 4 mIU/mL 30 minutes following an abbreviated GnRHa stimulation test at the Month 6 visit

  Leuprolide Acetate 45 mg will be considered effective for the treatment of children with CPP if ≥ 80% of subjects exhibit LH suppression < 4 mIU/mL at Month 6
- **Part B Extension**: the percentage of subjects with serum LH concentrations < 4 mIU/mL 30 minutes following an abbreviated GnRHa stimulation test at the Month 21 visit (5 months after the Injection #4 of leuprolide acetate)

Leuprolide acetate 45 mg will be considered effective for the treatment of children with CPP if ≥ 80% of subjects exhibit LH suppression < 4 mIU/mL at the Month 21 visit (5 months after the last of 4 administrations of the study drug)

NOTE: If Part B extension is conducted, the primary efficacy endpoint for Part A will become a secondary efficacy endpoint of Part B.

Secondary Efficacy Endpoint: Parts A & B

- The percentage of subjects with suppressed serum LH concentrations (< 4 mIU/mL) 30 minutes post GnRHa stimulation test at all assessed time points
- Changes in height velocity (growth rate), and bone age advancement will be evaluated relative to chronological age using descriptive statistics from baseline to end of study
- Changes in physical signs of puberty as measured by changes in Tanner stages from baseline to end of study

Exploratory Assessments: Parts A & B

- Bone age progression will be further evaluated using descriptive statistics and figures at all assessed timepoints. Changes in bone age progression will be described for each individual and for the ITT and PP population over the entire treatment period
- Descriptive statistics will be used to describe changes in physical signs of puberty as measured by changes in Tanner stages at each assessed timepoint. Changes in Tanner staging will be described for each individual and for the ITT and PP population over the entire treatment period.
- The percentage of subjects with LH (< 4 mIU/mL), FSH (< 2.5 mIU/mL), estradiol (< 20 pg/mL) or testosterone (< 30 ng/dL) suppression to prepubertal levels and serum leuprolide levels at all assessed timepoints
- Evaluation of the incidence rate of GnRH antagonist reports (see Section 8.5.1) that occurred within the 2 weeks (± 2 days) following first drug administration will be descriptively compared to the incidence rate within the 2 weeks (± 2 days) after each subsequent drug administration
- Evaluation of the incidence rate of GnRH antagonist reports that occurred within 2 weeks (± 2 days) following drug administration will be descriptively compared to the incidence rate within the 2 weeks (± 2 days) prior to each scheduled visit.

9.2.3 Pharmacokinetic and Pharmacodynamic Evaluations

Leuprolide concentrations from each assessment time will be listed and descriptively analyzed. "By subject" serum concentrations versus time will be plotted on both linear and log scales. The characteristics of the burst of leuprolide concentration will be statistically described by the serum concentrations of leuprolide that are collected in the first week after each administration. The steady-state or baseline concentrations will be the statistical description of the leuprolide concentration collected at each assessment point at least one month after the first administration and prior to any GnRHa stimulation test or prior to subsequent administration of the leuprolide 45 mg injection solution. An approximation of the AUC of the systemic leuprolide concentration between each dose and for the entire treatment period will be provided.

Each of the hormones assessed, and in particular, LH and FSH, and testosterone/estradiol will be statistically described for each assessment point and for changes in concentration from baseline values. The ratio of LH to FSH will be provided for each assessment point will be presented with an additional analysis of percent change from baseline for the ratio.

For each assessment point the LH suppression from the GnRHa stimulation test results will be statistically described for the LH concentration 30 minutes after the agonist administration and the percent change in the LH concentration after the GnRHa stimulation test will be statistically compared to the baseline concentration of the GnRHa tests administered prior to the first dose. Additionally, the LH concentration 30 minutes after the agonist administration will be statistically contrasted to the leuprolide concentration at each assessment point to provide an assessment of the PK/PD relationship. Similar comparisons will be conducted to evaluate the relationship of leuprolide to changes in serum concentrations of FSH and testosterone/estradiol.

9.2.4 Interim Analysis

An interim analysis of LH suppression from the GnRHa stimulation test results will be conducted after approximately 40% of the 40 subjects anticipated to complete 6 months of assessments have data through the Month 6 visit (N = approximately 16). Based on these data, if LH concentrations after the GnRHa stimulation test are suppressed to < 4 mIU/mL in < 85% of these subjects, then Part B of the study will be invoked. All subjects still undergoing therapy in the Part A of the study and those yet to enroll in the study, if eligible, will be asked to participate in the Part B extension study for additional dosing at shorter intervals. The progression to Part B extension will be based on evaluations by the DSMB and Sponsor. Subjects that progress to Part B of the study will be provided information about Part B in an ICF and Assent Form (if required), which will be signed by appropriate parent/guardian(s) and the subject.

9.2.5 Accounting for Missing Data

Imputation of missing data will not be performed for baseline, efficacy, and safety endpoints.

9.2.6 Safety Analyses

A listing of all AEs, including SAEs and events leading to discontinuation, will be provided. The Data Management team will compile a list of all AEs based on the information entered in the eCRF. This listing will be sent to TOLMAR and the CRO Safety Department for the proper reconciliation of the study and safety databases. These listings will include: event term as reported, event term as coded with the Medical Dictionary for Regulatory Activities (MedDRA version(s) will be documented in the final Clinical Study Report), start date, start time (only for events beginning on the day of the first injection), stop date, outcome, seriousness, severity, relationship to Investigational Product, and action taken with Investigational Product. AEs recorded after signing of the ICF/Assent but PRIOR to the first injection will be reported as non-TEAEs.

The number and percent of subjects reporting AEs will be tabulated. Summaries will be presented by body system organ class (SOC) and preferred term (PT), and further by severity and relationship to the study drug.

SAEs will be discussed within the clinical study report. Data collected pertaining to SAEs will be presented in data listings.

Continuous serum chemistry and hematology laboratory results will be summarized using mean, standard deviation, median, minimum, and maximum for each study visit, each cohort and each treatment cycle with each cohort. Urinalysis results by dipstick will be listed. Laboratory test results that are normal at Screening and become abnormal during treatment will be reported.

Vital signs will be summarized at each time point with mean, standard deviation, median, minimum, and maximum by each cohort and each treatment period with each cohort.

Other medical history data and the physical examination data will be tabulated.

Concomitant medications will be classified according to the World Health Organization (WHO) Drug Dictionary (version(s) will be documented in the final Clinical Study Report) and will be presented in data listings.

9.3 Subject Populations for Analysis

Safety population: All subjects providing consent/assent and who received at least one dose of the study drug.

ITT population: Subjects providing consent/assent who received at least one dose, fulfilled the protocol eligibility criteria, and provided at least one PD laboratory assessment post dosing.

PP population: Subjects who have received at least one dose of the study medication and have fulfilled the protocol in terms of eligibility, interventions and outcome assessments for at least 6 months.

10.STUDY MANAGEMENT

10.1 Posting of Information on Clinicaltrial.gov

Study information from this protocol will be posted on clinicaltrials.gov before the start of subject enrollment.

10.2 Site Regulatory Documents Required for Initiation

CRO will receive the following documents prior to the initiation of the study at each site:

- Completed, signed Form FDA 1572
- Current curricula vitae, signed and dated, for the Principal Investigator and Sub-Investigators named on Form FDA 1572
- Documentation of IRB/IEC approval of the study Protocol, Principal Investigator, and ICF
- Current IRB/IEC membership list or assurance number
- A copy of the Protocol signature page signed by the Principal Investigator
- Non-disclosure Agreements for the Principal Investigator and Sub-Investigators named on Form FDA 1572
- Debarment Certifications for the Principal Investigator and Sub-Investigators named on Form FDA 1572

- Financial Disclosure Statements for all individuals named on Form FDA 1572
- Additional documents may be collected per local regulatory requirements

10.3 Primary Source Documents

The Investigator will maintain adequate and accurate records for each subject who has appropriate consent/assent to participate in the study. Source documents such as hospital, clinic or office charts, laboratory reports, radiology reports, and signed ICF/Assent (if required) documents are to be included in the subject's study chart. The Investigator will document the informed consent/assent process in the source documents; including documentation that the ICF/Assent were signed prior to the subject's participation in the study and that a copy of the signed and personally dated ICF/Assent were provided to the parent/guardian(s) and subject, as appropriate.

The Investigator must maintain primary source documents supporting significant data for each subject's medical notes. These documents are considered source data and should include documentation of:

- Demographic information
- Evidence supporting the diagnosis/condition for which the subject is being studied
- General information supporting the subject's participation in the study
- General history and physical findings
- Hospitalization or Emergency Room records (if applicable)
- Each study visit by date, including any relevant findings/notes by the Investigator(s) or designee, occurrence (or lack) of AEs, and changes in medication usage, including the date and time infusion was started and ended
- Any additional visits during the study
- Any relevant telephone conversations with the subject regarding the study or possible AEs
- An original, signed ICF/Assent (if required) for study participation

The Investigator must also retain all subject-specific printouts/reports of tests and procedures performed as a requirement of the study. During monitoring visits the monitor will validate data in the eCRF against these sources of data.

10.4 Study Monitoring

This study will be closely monitored by the CRO throughout its duration. Monitoring will be in the form of personal visits with the Investigator and his/her staff as well as through other appropriate communications by telephone, FAX, email, or mail. It is the monitor's responsibility to inspect the eCRF at regular intervals throughout the study to verify the completeness, accuracy, and consistency of the data, and to verify adherence to the Protocol, current ICH-GCP guidelines, and any applicable local regulations.

All data must be available in source documents before entry into the eCRF, and all data entered into the eCRF will be source data verified. Data that is required according to this Protocol is to be recorded in the eCRF. For data collected with the EDC system, source data documentation is defined as the first place the data are recorded. All source documents must be retained and retrievable at the site in study specific files.

Every effort will be made to maintain the anonymity and confidentiality of subjects during this study. However, because of the experimental nature of this treatment, the Investigator agrees to allow representatives of the Sponsor as well as authorized representatives of the Regulatory Agencies, such as the FDA, to inspect the facilities used in this study and to inspect, for purposes of verification, the hospital or clinic records of all subjects enrolled into this study. The Investigator agrees to cooperate with the monitor to ensure that any problems detected during the course of these monitoring visits are resolved.

Medical supervision for the conduct of this Protocol is the responsibility of the Investigator. The Principal Investigator must name all Sub-Investigators and may delegate certain tasks to named Sub-Investigators qualified and trained to do such tasks, but retains the overall personal responsibility for adequate supervision of study staff and ensuring that the study is conducted properly and in accordance with the design and intent herein. The Investigator must ensure that there is adequate training for all staff participating in the conduct of the study, including any new staff joining the study after it has begun. The Investigator must ensure that he or she has sufficient time to properly conduct and supervise the clinical study, and should develop a plan for the supervision and oversight of the study. A document outlining the specifics of the delegation will be maintained at the investigational site, in the study files, and will be updated as appropriate.

Investigators are responsible for protecting the rights, safety, and welfare of subjects under their care during a clinical study (ICH E6 GCP Section 4). This responsibility should include:

- Providing adequate medical care to study subjects for any AEs, including clinically significant laboratory values, related to the study
- Providing decisions for medical care by a qualified physician who is an Investigator or Sub-Investigator for the study
- Conducting the study in compliance with the Protocol.

The Investigator should inform the subject's primary physician about the subject's participation in the study if the subject has a primary physician and the subject agrees to the primary physician being informed. The Investigator is responsible for ensuring that drugs and devices are available for treating possible medical emergencies. The Investigator is required to ensure compliance with respect to the investigational drug schedule, visit schedule, and procedures as required by the Protocol. The Investigator is responsible for ensuring that the study is conducted according to sound medical practices, following local regulatory compliance, and ICH-GCP.

The Investigator will be responsible for ensuring that an annual update is sent to the IRB/IEC and/or appropriate local review board to facilitate their continuing review of the study (ICH E6 ICH-GCP Sections 3 and 4.4) and that the IRB/IEC and/or appropriate local review board is informed about the end of the study. Copies of the update, subsequent approvals, and final letter

must be sent to the CRO. Copies of all correspondence (eg, letters, email) to and from the IRB/IEC and/or appropriate local review board must be kept on file at the site and be available for review by the Sponsor or Sponsor's representative during monitoring visits or audits.

10.5 Electronic Data Capture and Electronic Case Report Form

An electronic case report form (eCRF) is required to be completed for each individual subject. The eCRFs will be provided for transfer of all research data by site personnel from data source documentation to a computer database. Each responsible person at a site, the CRO, or Sponsor will have user access with a unique username and password, with permissions providing each person their needed access. Some personnel will have data entry, data review, and query resolution permissions, while others may only have data read permissions, based on their individual study roles.

Study monitors will verify computerized data against its source. Monitoring will be enhanced by computer-assisted data management identifying missing or possibly erroneous data as soon as data is entered into the EDC system. This approach will allow initial remote monitoring, and communication between study monitors and site personnel before and between site visits, and will expedite data review and cleaning. The flow of data from start to finish will be as follows: site personnel will enter subject data that meets all mandatory requirements per system edit checks, and will mark the data as complete, at which time the data will only be changeable via a query issued by the study monitor or data management group. Site personnel will respond to all queries. Study monitors will review, query and ultimately resolve those queries. The subject's data will then be locked by data management, with only read access provided to authorized personnel.

All study data are housed in a secure computing environment. The EDC system will include a complete audit trail of all data entry, monitoring, and query activity that is compliant with Health Insurance Portability and Accountability Act (HIPAA) and 21 CFR Part 11 requirements.

Study data required by study monitors, other authorized representatives of the Sponsor, and appropriate regulatory authority inspectors will be available through the EDC system during the study. At the end of the study, a compact disc with site-specific data information will be provided to each site for archiving.

All required study information must be entered into the EDC system. eCRFs are considered complete when all data fields are complete and acknowledged as correct by the Study Monitor. It is the Investigator's responsibility to ensure completion, accuracy, review, and approval of all eCRFs. The Principal Investigator must sign an Investigator's Statement at study completion for each subject to document that the Investigator has met these responsibilities.

10.6 Modifications to the Protocol

The procedures defined in the Protocol and eCRF will be carefully reviewed so that all parties involved with the study fully understand the Protocol. Only the Sponsor may initiate an amendment to the Protocol. Protocol amendments must be submitted and approved by the IRB/IEC prior to implementation.

Protocol deviations affecting the safety of the subjects or the integrity of the data and must be avoided. However, deviations from the Protocol may be made if necessary to eliminate apparent

immediate hazard(s) to a subject or subjects. In this instance, the Investigator must notify the CRO and the IRB/IEC immediately after the deviation. The Sponsor will evaluate the circumstance and determine if the issue is broad enough to warrant a Protocol Amendment. Other deviations from the protocol must be submitted by Investigator to the IRB/IEC per their reporting requirements. A missed telephone call at two weeks (14 days ±2 days) after each administration will be considered a minor protocol deviation and will not remove a subject from the PP population.

10.7 Maintenance and Retention of Records

The study will be conducted in compliance with ICH-GCP. Investigators will follow the procedures of 21 CFR 312.62 and ICH E6, "Good Clinical Practice: Consolidated Guideline", for retention of study records and data. It is the responsibility of the Investigator to maintain a comprehensive and centralized filing system of all relevant documentation.

Investigators will be instructed to retain all study records required by the Sponsor, in a secure and safe facility with limited access. Records are to be retained for at least 2 years after approval of the application or withdrawal of the application unless otherwise notified by the Sponsor. Study documents should be retained for a longer period if required by local regulatory requirements. If the Investigator retires, relocates, or withdraws from this responsibility, custody may be transferred to a person who will accept this responsibility. The Sponsor must be notified in writing of the name of the new custodian.

The records to be archived include all documents pertaining to subject information (eg, IRB/IEC correspondence, ICF, and HIPAA authorization form), receipt and return or destruction of Investigational Product, final signed eCRF casebooks including a copy of the audit trail, and correspondence with the CRO. No documents shall be destroyed without first notifying the Sponsor, and receiving confirmation of the notification by the Sponsor, at least 30 days prior to the planned date of destruction.

10.8 Audits and Inspections

During the course of the study and/or after it has been completed, one or more site audits may be conducted by authorized representatives of TOLMAR. The purpose of the audit would be to determine whether or not the study is being conducted and monitored in compliance with recognized ICH-GCP guidelines and regulations.

Additionally, the study may be inspected by regulatory agencies. These inspections may take place at any time during the study or after completion of the study and are based on the local regulations.

10.9 Completion of the Study

The Principal Investigator for each participating site must submit a final report to TOLMAR and IRB/IEC within 12 months of study completion or termination.

11.CONFIDENTIALITY, USE OF INFORMATION, AND PUBLICATION

11.1 Confidentiality

During the course of the study, user access to the files with subject identifiers and files with study outcomes will be restricted to core staff with any exceptions to be approved by the Principal Investigator.

In addition to the use of passwords and other security measures, all documents containing identifying information on individuals or physicians are considered confidential materials and will be safeguarded to the greatest possible extent.

11.2 Disclosure of Information

Information concerning the study, patent applications, processes, scientific data, or other pertinent information is confidential and remains the property of TOLMAR. The Investigator may use this information for the purposes of the study only.

It is understood by the Investigator that the Sponsor will use information developed in this clinical study in connection with the development and marketing of TOLMAR formulation and, therefore, the Sponsor may disclose study information, as required, to other clinical investigators and to regulatory agencies. In order to allow the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

11.3 Publication

The Investigator shall not make any publication related to this study without the express written permission of the Sponsor. Should the Investigator wish to publish or present the results of this study, the Investigator agrees to provide the Sponsor with an abstract, manuscript, and/or presentation for review 90 days prior to submission for publication/presentation. The Sponsor retains the right to delete from the manuscript confidential information and to object to suggested publication and/or its timing (at the Sponsor’s sole discretion).

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13.APPENDICES

13.1 Clinical Laboratory Parameters

All hematology and clinical chemistry parameters as well as the listed screening tests will be analyzed at a central laboratory. Urinalysis parameters, assessed by dipsticks, will be analyzed locally using provided kits. Sample for clinical laboratory tests will be collected at times specified in Table 2 Blood Sampling Times by Parameter for Visit 1—Part A.

Hematology

Platelet Count	*RBC Indices*:	*Automated WBC Differential:*
RBC Count	MCV	Neutrophils
WBC Count (absolute)	MCH	Lymphocytes
Reticulocyte Count	MCHC	Monocytes
Hemoglobin		Eosinophils
Hematocrit		Basophils

Clinical Chemistry

Urea	Potassium	AST (SGOT)	Total and direct bilirubin
Creatinine	Chloride	ALT (SGPT)	Uric Acid
Glucose	Total CO_2	GGT	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein

Other Parameters

HBsAg (Hepatitis B Surface Antigen);
HCVAb (Hepatitis C antibody)
Pregnancy test (urine)
Fasting serum lipid measurements to include: total cholesterol, HDL, LDL, triglycerides

Urinalysis

pH, glucose, protein, blood and ketones by dipstick provided by sponsor

13.2 Tanner Stages

The Tanner stages, developed by Marshall and Tanner (1969) is a commonly used system to categorize pubertal maturation in terms of sequence, timing and tempo as described below.

Boys - development of external genitalia

Stage 1: Prepubertal
Stage 2: Enlargement of scrotum and testes; scrotum skin reddens and changes in texture
Stage 3: Enlargement of penis (length at first); further growth of testes
Stage 4: Increased size of penis with growth in breadth and development of glans; testes and scrotum larger, scrotum skin darker
Stage 5: Adult genitalia

Girls - breast development

Stage 1: Prepubertal
Stage 2: Breast bud stage with elevation of breast and papilla; enlargement of areola
Stage 3: Further enlargement of breast and areola; no separation of their contour
Stage 4: Areola and papilla form a secondary mound above level of breast
Stage 5: Mature stage: projection of papilla only, related to recession of areola

Boys and girls - pubic hair

Stage 1: Prepubertal (can see velus hair similar to abdominal wall)
Stage 2: Sparse growth of long, slightly pigmented hair, straight or curled, at base of penis or along labia
Stage 3: Darker, coarser and more curled hair, spreading sparsely over junction of pubes
Stage 4: Hair adult in type, but covering smaller area than in adult; no spread to medial surface of thighs
Stage 5: Adult in type and quantity, with horizontal distribution ("feminine")