Statistical Analysis Plan

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

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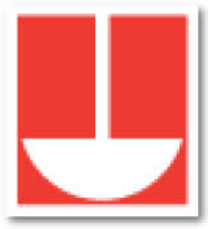

TOLMAR Inc.

STATISTICAL ANALYSIS PLAN

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

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3. LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION OR DESCRIPTION
°C	Degree Celsius
°F	Degree Fahrenheit
ADaM	CDISC Analysis Dataset Model
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase or SGPT
AST	Aspartate transaminase or SGOT
ATC	Anatomical Therapeutic Chemical
AUC	Area under the Serum Concentration-Time Curve
CDISC	Clinical Data Interchange Standards Consortium
C_{max}	Maximum drug concentration
CPP	Central Precocious Puberty
CSR	Clinical study report
CV	Coefficient of Variation
DD	Day
dL	deciliter
EMEA	European Medicines Agency
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GnRH	Gonadotropin Releasing Hormone
GnRHa	Gonadotropin Releasing Hormone Agonist
ICH	International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use
ICF	Informed Consent Form
kg	Kilogram(s)
LH	Luteinizing Hormone
MedDRA®	Medical Dictionary for Regulatory Activities
mIU	Milli International Units
mL	Milliliter(s)
mm Hg	Millimeters of Mercury
N	Sample Size
ng	Nanogram

PD	Pharmacodynamic
PE	Physical Examination
pg	Picogram
PK	Pharmacokinetic
PP	Per-protocol [population]
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
SD	Standard deviation
SDTM	Study Data Tabulation Model
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
T_{max}	Time of maximum (peak) drug concentration
ULRR	Upper limit of the reference range
WHO-Drug	World Health organization

4. BACKGROUND AND PURPOSE

This Statistical Analysis Plan (SAP) describes the planned procedures and analyses for TOLMAR study TOL2581A: *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*. This study is a multicenter, open-label, single-arm, adaptive, interventional study to assess efficacy, safety and pharmacokinetics/pharmacodynamics with up to two study phases (Part A and Part B) distinguished by dosing schedule.

This SAP is compliant with the principles set forth in guidance documents by the Food and Drug Administration (FDA), the European Medicines Agency (EMEA), the American Statistical Association[i], the Royal Statistical Society[ii] and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials (E9)[iii].

Additional analyses and modifications to those found in this SAP will be allowed. Any such changes that are added *prior to examination of the data by the statistician* will be listed in a future appendix to this document (i.e., Appendix 4). Procedures in the final version of this SAP and the noted appendix may be referenced as *a priori* in documents describing the safety, efficacy and pharmacokinetics outcomes of TOLMAR Study TOL2581A. Any statistical analyses for Study TOL2581A that fall outside those described in the final version of this SAP and the noted appendix will be designated as "post hoc".

To ensure that the evaluative data for this study are accurate, edit checks will be described in and implemented according to a Data Management Plan.

This SAP assumes reader familiarity with the Study TOL2581A protocol and any protocol amendments.

5. STUDY OBJECTIVES

5.1. Primary Objective

The primary objective of this study is to determine the effectiveness of leuprolide acetate 45 mg for injectable suspension for the treatment of children with central precocious puberty (CPP).

5.2. Secondary Objectives

The secondary objectives of this study are to:

- 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 testosterone/estradiol;
- Assess percent change from baseline in height and bone age after the first treatment administration;
- Assess growth velocity of height in cm/year after the first treatment administration;
- Assess changes in physical signs of puberty as measured by changes in Tanner stages or in changes or onset of menses; and
- 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 permits.

6. STUDY METHODS

6.1. Overall Study Design and Plan

6.1.1. Criterion for an Adaptive Change in Design

This multicenter, open-label, single-arm, adaptive, interventional study potentially has two parts with Part B contingent upon the outcome of Part A. *Whether or not Part B is to be invoked will be decided as follows.* When approximately 16 subjects enrolled in the study reach Month 6, the stimulation data from these subjects will be evaluated to determine if LH concentration at 30 minutes after GnRHa stimulation is suppressed to < 4 mIU/mL.

1) If ≥ 85% of these first subjects are suppressed at 6 months then Part B will *not* be invoked and all subjects will be seen through the final planned Part A visit (i.e., Visit 8).

2) If approximately < 85% of subjects (N ≥ 3) exhibit suppression the study will immediately proceed to Part B. If Part B is invoked subjects currently enrolled in Part A and have not yet received a 2nd injection, will be entered into Part B on Visit 7. Then, all future subjects enrolled in the study will undergo the equivalent of Visits 1 through 6 of Part A followed by Part B beginning on Visit 7.

6.1.2. Design and Procedures for Part A and Part B

Subjects enrolled in Part A will receive their first injection on Visit 1 (Day 0). Part A will continue over 12 months with Visits 2, 3, 4, 5, 6, 7 and 8 respectively planned at Months 1, 3, 5, 6, 9, 11 and 12. Part B *if invoked* is planned over an additional 10 months and will begin at Visit 7 of Part A and continue through Visits 8, 9, 10 and 11 which shall correspond to Months 15, 16, 20 and 21.

Whether or not Part B is invoked, all subjects under Part A will receive a first treatment injection at Visit 1 (Day 0); and a second injection at Visit 5 (Month 6). If Part B is invoked then all subjects additionally will experience treatment injections on Visit 7 (Month 11) and Visit 9 (Month 16) under Part B. If only Part A is completed, the percent of subjects with suppression at 30 minutes after GnRHa stimulation of < 4 mIU/mL at six (6) months will constitute the primary outcome variable. If part B is invoked, the primary outcome variable will be the percent of subjects with suppression at twenty-one (21) months.

The planned visits and data to be collected under Part A and under Part B (if invoked) are presented in the schematics that follow.

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 0.5**	**~Month 1**	**~Month 3**	**~Month 5**	**~Month 6**	**~Month 6.5**	**~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
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	
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

[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 are 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 0.5	~Month 1	~Month 3	~Month 5	~Month 6	~Month 6.5	~Month 9	~Month 11	~Month 12	
Hepatitis B antigen/Hepatitis C antibody	X											
Serum lipids – fasting	X	X										

Table 1 Schedule of Assessments—Part A (continued)

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 0.5	~Month 1	~Month 3	~Month 5	~Month 6	~Month 6.5	~Month 9	~Month 11	~Month 12	
LH and FSH samples (basal)	X	See Table 2		X	X	X	X		X	X	X	X
Testosterone/estradiol samples (basal)	X	See Table 2		X	X	X	X		X	X	X	X
Serum Leuprolide samples (basal) [2]	X	See Table 2		X	X	X	X		X	X	X	X
GnRHa Stimulation (SC leuprolide acetate) [3]	X				X		X		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] Blood samples for leuprolide serum concentrations must be collected BEFORE the GnRHa stimulation test.
[3] 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 8.1.14.

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 0.5	~Month 1	~Month 3	~Month 5	~Month 6	~Month 6.5	~Month 9	~Month 11	~Month 12	
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 [4]		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)

[4] 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 [1]	X							
Complete Physical Examination							X	X
Query Subject: How have you felt in 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 [2]	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)[3]	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 [4]	X			X				
Adverse Events Assessment	X		X	X		X	X	X
Schedule/Confirm Next Visit	X		X	X		X		(X)

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

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

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

[4] 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.

6.2. Selection of Study Population

Children falling within the following profile will be entered into the study: females age 2 to 8 years (inclusive) or males age 2 to 9 years (inclusive); confirmed diagnosis of CPP within 12 months of Baseline Visit (Day 0) but have not received prior GnRH agonist treatment for CPP; pubertal-type LH response following an Abbreviated GnRHa Stimulation Test before treatment initiation > 5 mIU/mL; clinical evidence of puberty, defined as Tanner stage ≥ 2 for breast development in females or testicular volume ≥ 4 mL in males; and difference between bone age (Greulich and Pyle method) and chronological age ≥ 1 year.

6.3. Treatment and Random Assignment

This single arm study does not require the use of randomization. All subjects will be treated identically with respect to procedures carried out in either Part A or Part B of this study.

6.4. Treatment Masking (Blinding)

This is an open label study. Neither subjects, the sponsor or study staff are blind to the treatment.

6.5. Analyses and Reporting

In this study both *a) the need for an adaptive change in study design* and *b) treatment efficacy* will be based on an absolute descriptive finding rather than an inferential significance level.

6.6. Criterion for Treatment Efficacy

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 children at six months, namely, percent of children with < 4 mIU/mL suppression, will *also* function as the primary outcome variable when applied to all children in the study. As was the case for evaluating the requirement for an adaptive change in design, an absolute descriptive rather than inferential statistical outcome will be used to assess efficacy for the primary outcome variable. Using the same variable as that used to omit or invoke Part B, efficacy will be claimed if ≥ 80% of the children exhibit < 4 mIU/mL suppression.

If suppression in approximately < 85% of the first 16 subjects (N ≥ 3) 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 children in the study at Visit 11 (Month 21) is found, efficacy will be claimed. The primary variable if only Part A of the study were carried out will then become a secondary outcome variable.

6.7. Sample Size Determination

The expected final sample size is between 25 and 50 subjects, depending on dropout rate and whether the study is prolonged by the inclusion of Part B. If for the final sample size ≥ 80% of

subjects exhibit < 4 mIU/mL suppression, efficacy will be claimed. It is actually expected that 85% to 90% response is likely. The table immediately below shows the lower one-sided 95% confidence limits for final sample sizes varying from 25 to 50 in increments of five subjects under the expectations of 85% suppression and 90% suppression.

Table 4 Numeric Results for One-Sided Lower-Limit Confidence Intervals for One Proportion Confidence Interval Formula: Simple Asymptotic with Continuity Correction[1]

Confidence Level	Sample Size (N)	Actual Distance from P to Lower Limit	Proportion (P)	Lower Limit	Upper Limit
0.950	25	0.137	0.850	0.713	1
0.950	25	0.119	0.900	0.781	1
0.950	30	0.124	0.850	0.726	1
0.950	30	0.107	0.900	0.793	1
0.950	35	0.114	0.850	0.736	1
0.950	35	0.098	0.900	0.802	1
0.950	40	0.105	0.850	0.745	1
0.950	40	0.091	0.900	0.809	1
0.950	45	0.099	0.850	0.751	1
0.950	45	0.085	0.900	0.815	1
0.950	50	0.093	0.850	0.757	1
0.950	50	0.080	0.900	0.820	1

In Table 4 the lower one sided confidence limit never falls below 70%. Suppression to < 4 mIU/mL in 70% of the subjects is considered to be clinically important by TOLMAR. Thus the sample size is thought to be adequate.

7. PLANNED STUDY ANALYSES

Statistical analyses for this study will be comprised of descriptive statistics presented over time or at predesignated time points of special interest. Baseline, efficacy, safety and PK endpoints will be evaluated using descriptive statistics. For example, comparisons between two time points will be carried out by contrasting descriptive outcomes that exist for each of those time points.

Descriptive evaluation will in general take one of four forms depending on the underlying metric of the variable under analysis.

1) If the metric is categorical the following information at minimum will be provided: count (numerator), base (denominator) and percentage (numerator/denominator) for each category and overall. For dichotomous categorical variables, confidence intervals may in

[1] Hintze, J. (2014). PASS 13. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com.

selected instances be provided. The term used hereafter to denote this type of analysis will be *categorical descriptive analysis*.

2) If the metric is continuous or presumed continuous the following information at minimum will be provided: number of subjects, mean, standard deviation, coefficient of variation, minimum and maximum. Confidence intervals may in some instances be provided. The term used hereafter to denote this type of analysis will be *continuous descriptive analysis.*

3) Categorical variables compared across time may be presented as a shift table. For example, a laboratory test result could be normal, low abnormal or high abnormal. A shift table comparing values between baseline and end-of-study would show the number and percent of subjects with shift outcomes of the form normal to normal, normal to low abnormal, normal to high abnormal, high abnormal to normal, high abnormal to low abnormal, high abnormal to high abnormal, low abnormal to normal, low abnormal to low abnormal, and low abnormal to high abnormal. A simpler version of the table that omits direction of abnormality might be normal to normal, normal to abnormal, abnormal to normal, abnormal to abnormal. The term used hereafter to denote this type of analysis will be *shift table analysis*.

4) Serum concentrations will be analyzed by evaluating concentration at each time point using continuous descriptive analysis; and by evaluating the PK parameters AUC, Cmax and Tmax using continuous descriptive analysis. Since the PK sampling frequency in this trial is limited due to the age of the subjects, it will be expected that the PK parameters will have larger intra-patient variability. Concentration plots in the original and log scale will be created, combined over subjects and by subject. Continuous descriptive analysis will be provided for absolute values of AUC, Cmax and Tmax as well as log transformed values of these parameters. All together the above analyses in part or whole will be referred to as *PK analysis*.

Because this study collects data at many interim time points, extensive use of graphs to display categorical descriptive analysis results and continuous descriptive analysis results over time will be employed. This will facilitate an assessment of trend.

Further note that because tables containing categorical descriptive analysis and continuous descriptive analysis will exist for the various outcome parameters at each time point, selected time points of interest can be compared to each other for a specific purpose. For example, the medical writer can compare descriptive outcomes at visits after injection 2 to visits after injection 4 to evaluate GnRHa simulation results under a six and a five month injection separation schedule. Using specific comparisons of descriptive statistics at designated time points, objectives for the assessment of efficacy (see Protocol Section 9.2.2: Efficacy Evaluations) can be accommodated.

Plots of individual subject outcomes will be generated for all variable concentrations used in the PK/PD analyses (Leuprolide, LH, FSH, testosterone and estradiol concentration), bone age and height.

The table that follows summarizes the planned analyses for baseline, efficacy, safety and PK variables.

Table 5 Type of Analysis Applied to Baseline, Efficacy, Safety and PK Variables

Variable Class	Variable(s)	Analysis				Listed/Not Analyzed[1]	Time Points Analyzed (Visits)[2]
		Categorical Descriptive Analysis	Continuous Descriptive Analysis	Shift Table Analysis	PK Analysis		
Baseline	Presence of Informed Consent	x					Screening, Visit 7
Baseline	Inclusion/Exclusion Criteria	x					Screening
Baseline	Demographics (categorical)	x					Screening
Baseline	Demographics (continuous)		x				Screening
Baseline	Medical History (categorical)	x					Screening
Baseline	Medical History (descriptive)					x	Screening
Baseline	Meds/Treatments History					x	Screening
Baseline, Safety	Vital Signs		x				Screening, All Visits
Baseline, Safety	Weight		x				Screening, All Visits
Baseline, Efficacy	Height		x				Screening, All Visits
Baseline, Safety	Complete Physical Exam (categorical)	x					Screening, Visit 11
Baseline, Safety	Complete Physical Exam (descriptive)					x	Screening, Visit 11
Safety	Directed Physical Exam (categorical)	x					Visits 1, 2,3,5,6,7,8, 9 10
Safety	Directed Physical Exam (descriptive)					x	Visits 1, 2,3,5,6,7,8, 9 10

[1] All collected and derived variable values will be in listings. However, this column highlights information that is closely related to information found in an adjacent row of this table; will not be descriptively analyzed; but will be presented in a listing.
[2] This table assumes that Part B will be invoked. If Part B is not invoked visits will be altered to conform to the *Schedule of Assessments: Part A*.

Variable Class	Variable(s)	Analysis				Listed/Not Analyzed[1]	Time Points Analyzed (Visits)[2]
		Categorical Descriptive Analysis	Continuous Descriptive Analysis	Shift Table Analysis	PK Analysis		
Safety	Flare Symptoms	x	x[3]				Telephone interview weeks 26 & 46, Visits 2-11
Safety	Pregnancy Test	x					Visits 1, 5,7, 9, 11
Safety	Adverse Events	Reported in Listings and Summarized in Tabulations[4]					Throughout Study
Baseline, Safety	Laboratory Tests[5]	x	x	x			Screening, All Visits
Baseline	Hepatitis B/C Antibody	x		x			
Baseline, Safety	Serum Lipids (fasting)	x	x				Screening, Visits 1,7
Efficacy	Leuprolide, LH, FSH, Testosterone, Estradiol (basal)		x		x		Screening, All Visits
Efficacy	LH, FSH, Testosterone, Estradiol (GnRHa stimulation)[6]	x	x				Screening, All Visits
PK	Serum Leuprolide (basal)		x		x		Screening, All Visits
Efficacy	Tanner Staging[7] and Menses Presence or Change	x	x	x			Screening, Visits 3, 5, 7, 8, 9, 10, 11
Efficacy	All Exploratory Efficacy Endpoints[8]	x	x				Screening, All Visits

[3] See Appendix 3: Global Interview Symptom Assessment. Each item will be analyzed separately using categorical descriptive analysis. A count of total number of symptoms will be analyzed using continuous descriptive analysis.
[4] AEs will be coded using MedDRA which in turn will allow quantification of events. Number and percent of subjects reporting AEs will be tabulated for the Safety Population. Tabular summaries will be presented by System Organ Class (SOC) and Preferred Term (PT), and further by severity and relationship to the investigational product. In summaries of severity, subjects who reported more than one event that are mapped to the same SOC and/or PT will be counted only once under the strongest severity. In summaries of relationship, subjects who reported more than one event that are mapped to the same SOC and/or PT will be counted only once under each applicable relationship.
[5] Laboratory values include urinalysis, hematology and chemistry. Data are predominately continuous with a few categorical scales.
[6] For these variables a dichotomy will be evaluated (LH < 4 mIU/mL, FSH < 2.5 mIU/mL, estradiol < 20 pg/mL, testosterone < 30 ng/dL) using categorical descriptive analysis.
[7] Each five stage rating will be treated as a categorical scale and as a presumed continuous scale. Respectively, these will be analyzed using categorical descriptive analysis and continuous descriptive analysis. Categorical descriptive analysis will be applied to menses presence and menses change. Baseline to end-of-study stage shift tables for each Tanner category will be constructed.
[8] Exploratory efficacy endpoints are described in the Exploratory Efficacy Endpoint section. Some endpoints are categorical and others continuous, thus both categorical descriptive analysis and continuous descriptive analysis will be required.

8. BASELINE INFORMATION AND TREATMENT EMERGENT EFFICACY, PHARMACOKINETIC AND SAFETY ENDPOINTS

Baseline, efficacy, pharmacokinetic (PK) and safety information to be collected as described below.

8.1. Baseline and Related Information

Some baseline variables in the sub-sections to follow may also serve as efficacy, safety and PK endpoints when captured post treatment. In such instances, variables may be located in more than one section of this SAP.

The variables that will be used to characterize study subjects at baseline are presented below.

8.1.1. Demographic Information

Demographic characteristics will be collected, 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*).

8.1.2. 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.

8.1.3. Prior and Concomitant Medications and 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.

8.1.4. 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).

8.1.5. Weight

Body weight (kg) will be measured.

8.1.6. Height

Standing height will be recorded with a calibrated stadiometer (e.g., "Harpenden" stadiometer) that has increments in millimeters (mm) and a functional Frankfort Plane perpendicular to the standing surface. The Frankfort Plane will be used on the stadiometer to determine the actual standing height to ± 1 mm.

8.1.7. 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.

8.1.8. Tanner Stages and Menses

Sexual development in puberty will be assessed by Tanner staging, a system developed by Marshall and Tanner[iv] to categorize pubertal maturation. See Appendix 1 for details on the Tanner stages. The presence of menses and any change in menses will be collected.

8.1.9. Clinical Laboratory Assessments

Clinical laboratory assessments (hematology, clinical chemistry, fasting serum lipids, hepatitis B & C, and urinalysis parameters) are listed in Appendix 2. 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.

8.1.10. 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.

8.1.11. Hand and Wrist X-Ray (Bone Age)

A single X-ray of the non-dominant hand and wrist will be obtained to determine bone age using a Greulich and Pyle Atlas. Although a local reader will determine study eligibility during screening, X-rays will be sent to a blinded central reader for the bone age evaluations that will be analyzed.

8.1.12. Basal LH, FSH, Testosterone/Estradiol Concentrations

Blood samples for serum LH, FSH, testosterone (males) / estradiol (females) concentrations (as appropriate) will be collected and analyzed by a central laboratory according to current validated

assays. All samples will be obtained before each study drug injection and before GnRHa stimulation tests. A central laboratory will be used.

8.1.13. Abbreviated GnRHa Stimulation Test

Baseline blood samples for serum LH, FSH, and testosterone/estradiol concentrations will be obtained prior to the start of a 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.

8.1.14. Pharmacokinetic Assessment

Blood samples for analysis of leuprolide concentrations as well as basal LH, FSH, testosterone and estradiol concentrations will be processed by a central bioanalytical laboratory. Date and time of each sample will be recorded.

8.2. Efficacy Endpoints and Assessments

8.2.1. Primary Efficacy Endpoints and Assessments

As described in the Study Methods section, subjects will at minimum undergo Part A of the study where two treatment injections separated by six months will be given starting at Visit 1 (Day 0); an Abbreviated GnRHa Stimulation Test six months after a subject's first treatment injection will be used to determine treatment efficacy; and a 12 month follow-up will occur. Alternatively subjects will undergo the first six visits of Part A and then at Visit 7 (Month 11) undergo Part B of the study (if invoked). In Part B of the study an additional two treatment injections separated by 5 months will be given starting at Visit 7 (Month 11), and an GnRHa Stimulation Test five months after the fourth treatment injection (i.e., at the 21st month visit) will be used to determine treatment efficacy at the end of the study. Two primary endpoints are defined contingent upon the invocation of Part B.

- If only Part A is carried out, the primary endpoint is defined as the percentage of subjects with serum LH concentrations < 4 mIU/mL at 30 minutes following an abbreviated GnRHa Stimulation Test at Visit 5 (Month 6). LH concentrations < 4 mIU/mL are considered prepubertal. The Investigational Product, 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 6 visit.

- If Part B is invoked, the primary endpoint is defined as the percentage of subjects with serum LH concentrations < 4 mIU/mL at 30 minutes following an abbreviated GnRHa Stimulation Test at Visit 11 (Month 21). 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.

8.2.2. Secondary Efficacy Endpoints and Assessments

Serving as secondary endpoints will be the following variables.

- The percentage of subjects with serum LH concentrations < 4 mIU/mL at 30 minutes following an abbreviated GnRHa Stimulation Test for any available measurement other than the measurement constituting the primary outcome variable (see above).
- The percent change from baseline in height at each available post-baseline measurement. Percent change is defined as (((change from Baseline)/(Baseline)) x 100).
- The growth velocity of height in cm/year at each available post-baseline measurement. Growth velocity is defined for each visit as (change from Baseline)/[(number of weeks since Baseline)/52)].
- The ratio of bone age at each given measurement point to chronological age at the same measurement points.
- Baseline to end-of-study stage shifts for each Tanner category.
- The percent change from baseline in hormonal concentration (LH, FSH, Testosterone, and Estradiol) at each available post-baseline measurement. Percent change is defined as (((change from baseline)/(baseline)) x 100).
- The percent change from baseline in systemic leuprolide concentration at each available post-baseline measurement. Percent change is defined as (((change from baseline)/(baseline)) x 100).

8.2.3. Exploratory Efficacy Endpoints and Assessments

The following exploratory efficacy endpoints will be evaluated.

- Height at each available measurement point.
- Bone age at each available measurement point.
- Bone age progression at each available post-baseline measurement point. Bone age progression is defined as (((change from baseline)/(baseline)) x 100), which is percent change from baseline.
- Ratio of bone age at a given measurement point to chronological age at start of study.
- A GnRH Antagonist Evaluation will occur for the two week period following each treatment (see Appendix 3) and at each visit to assess flare symptoms. The percent of subjects who affirm (or whose parent/guardian affirms) each symptom domain in the global interview will be obtained. Percentages will be compared across all available time points to assess trend. Focused pairwise comparisons will occur between the outcome 2 weeks (± 2 days) after the first injection and each of the outcomes 2 weeks (± 2 days) after subsequent injections; and outcomes at 2 weeks (± 2 days) after each injection and the corresponding nearest adjacent outcome in the two weeks (± 2 days) *prior* to each scheduled visit.
- Percent of subjects exhibiting each stage of each Tanner category across all available time points to assess trend.
- The percentage of subjects with FSH, estradiol and testosterone suppression to prepubertal levels (FSH < 2.5 mIU/mL, estradiol < 20 pg/mL and testosterone < 30 ng/dL) at each available time point.
- For each basal hormone (LH, FSH, Testosterone, and estradiol) at each available time point the following will be presented: a) a plot of the mean and standard deviation over time points; b) a plot of the mean and standard deviation of the change from baseline

(screening) over time points; c) a time point by individual concentration scatterplot; and d) a time by percent subjects at prepubertal level histogram plot.
- Changes in the ratio of LH/FSH at each time point including baseline.

8.3. Pharmacokinetic/Pharmacodynamic Endpoints and Assessments

The primary pharmacokinetic (PK) endpoint is Leuprolide concentration. Secondary PD endpoints are the changes in LH, FSH, testosterone and estradiol concentrations due to the leuprolide acetate injections. At Visit 1 concentration at multiple time points will be collected at ≥ 30 minutes prior to treatment injection, and at 1 hours (± 5 minutes), 4 hours (± 10 minutes) and at 6 hours (± 15 minutes) after treatment injection. Basal concentration at a single time point per visit will be collected within a 28 day screening period and at all visits subsequent to Visit 1.

8.3.1. PK/PD Parameters

The following *PK/PD parameters will serve as endpoints.*

- *Visit 1 (baseline, 1 hr, 4 hrs, 6 hrs)*
    - Concentration Value at each time point
    - AUC over six hours
    - Cmax over six hours
    - Tmax over six hours

- *Basal Measurement over Study Period (Screening, first Visit 1 measurement, Visit 2 and greater)*
    - Concentration Value at each visit
    - AUC (over study period (i.e., 0 to infinity))
    - AUC (over set time periods (e.g. 0 to 6 hours, 0 to 6 mo, Day 7 to 6 mo))
    - Cmax (post each treatment administration)
    - Tmax (post each treatment administration)

- *Post GnRHa stimulation (*screening; Visits 3, 5, 6 and 8 in Part A; Visits 7, 9 and 11 in Part B)*)*
    - Concentration Value of LH post 30 min of test initiation

8.3.2. PK/PD Analyses

Analysis for each PK/PD variable will include the following.

- Serum concentrations will be analyzed by evaluating concentration at each time point using continuous descriptive analysis; and by evaluating the PK parameters AUC, Cmax and Tmax using continuous descriptive analysis. This will be done for Visit 1 time points and for basal time points.

- Concentration plots in the original and log scale will be created, combined over subjects (mean and standard deviation) and by subject.

- Additional continuous descriptive analysis will be provided for log transformed values of the PK parameters.

- Burst leuprolide concentrations will be evaluated by examining PK measurements over the first 6 hours post injection.

- Steady state will be evaluated by examining together the leuprolide concentrations collected at each assessment point that are at least one month after the first administration and prior to any Abbreviated GnRHa Stimulation Test or prior to subsequent administration of the leuprolide 45 mg injection solution.

- Change from baseline (screening) for post-baseline basal concentration values will be computed, submitted to continuous descriptive analysis and plotted over each non-baseline time point. Two plots will be created. One will contain means and standard deviations by time point. The second will be a scatterplot displaying individual values at each time point.

- The ratio between prior basal and post GnRHa stimulation concentration will be computed at each available time point, submitted to continuous descriptive analysis and plotted over time points. Two plots will be created. One will contain means and standard deviations by time point. The second will be a scatterplot displaying individual values at each time point.

- The ratio between the basal concentration at screening and post GnRHa stimulation concentration will be computed at each available time point, submitted to continuous descriptive analysis and plotted over time points. Two plots will be created. One will contain means and standard deviations by time point. The second will be a scatterplot displaying individual values at each time point.

- The basal LH to FSH ratio will be computed for each available time point and plotted; and percent change from baseline for this ratio will be computed and plotted. Two plots will be created. One will contain means and standard deviations by time point. The second will be a scatterplot displaying individual values at each time point.

- Further analysis will be accomplished using scatter plots. The pairwise relationship between the various PK/PD variables (leuprolide, LH, FSH, testosterone and estradiol serum concentration) will be captured in scatter plots that use mean concentration values, geometric mean concentration values and individual subject concentration values.

9. SAFETY ASSESSMENTS

Selected endpoints described under "Baseline and Related information" also will serve as safety parameters. These endpoints are included in the list below.

- Vital Signs
- Weight
- Physical Examination
- Clinical Laboratory Assessments
- Pregnancy Test
- Adverse Events
- Serious Adverse Events

Categorical descriptive analysis, continuous descriptive analysis and shift table analysis will be applied to safety endpoints as described in Section 7: Planned Study Analyses.

10. ANALYSIS POPULATIONS

10.1. Safety population

The safety population will consist of all subjects providing consent/assent and who received at least one dose of the study drug.

10.2. ITT population

The intent to treat (ITT) population will consist of 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.

10.3. PP population

The per protocol population (PP) will consist of 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.

The table below cross-classifies the various endpoints with the analysis populations.

Table 6 Cross-classification of Various Endpoints with the Analysis Populations

Type of Endpoint	Study Population		
	Safety	Intent to Treat	Per Protocol
Baseline Endpoints		x	x
Primary Efficacy Endpoint		x	x
Secondary Efficacy Endpoint		x	x
Exploratory Efficacy Endpoints		x	x

Safety Endpoints	x		
PK Endpoints		x	

Efficacy will be based on findings using the ITT population. It is noted that for some variables the ITT and PP populations may be identical.

11. GENERAL CONSIDERATIONS

11.1. Significance Testing

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. Inferential statistical testing will not be provided. Rather, descriptive outcomes for the primary and secondary efficacy variables will be used to evaluate the efficacy of this treatment. If requested by the medical writer or the FDA reviewer, inferential significance levels will be formally provided on an *as needed* basis.

11.2. Continuous and Presumed Continuous Data

Throughout the study, variables that fall on scales that are or can be presumed to represent continuous dimensions will be captured. Standard descriptive statistics (number of subjects, mean, standard deviation, coefficient of variation, minimum value and maximum value) will be used to characterize continuous and presumed continuous data. In general minimum and maximum will be reported to the numbers of decimal digits as recorded for the original (observed) data; the mean and median will be reported to one decimal digit more than in the original (observed) data; the standard deviation will be reported to two decimal digits; and the coefficient of variation percentage (CV %) will be quoted to one decimal digit.

11.3. Categorical Data

Some variables in this study will be captured in the form of a categorical scale. Frequency distributions (number [n] and percentage of subjects [%] for each category) will be used to summarize categorical variables. In general, percentages will be reported to one decimal digit.

11.4. Statistical Software

All analyses will be performed using SAS® Software version 9.2 or later.

12. IMPUTATION AND MISSING DATA

Unless otherwise indicated, imputation of missing data will not be performed for baseline, efficacy and safety variable values. Each table containing an analysis that reflects an outcome at a given time point in the study will contain only subjects in the analysis population under examination who have data available at that time point.

If a missing concentration datum is surrounded by non-missing values, interpolation will be used in the calculation of AUC, Cmax and Tmax. Otherwise, the nearest non-missing point in time will be used.

If missing date and time values are evident in data not used to develop PK parameters, the following missing date and time algorithm may be applied.

For partial start date/time:

- If the year is unknown, then the date will not be imputed and will be assigned a missing value.
- If the month is unknown, then:
  - If the year matches the year of the dose of study drug date, then the month and day of the dose of study drug date will be imputed.
  - Otherwise, 'January' (01) will be assigned.
- If the day is unknown, then:
  - If the month and year match the month and year of the dose of study drug date, then the day of the dose of study drug date will be imputed.
  - Otherwise, '01' will be assigned.
- If the day is unknown, then:
  - If the month and year match the month and year of the dose of study drug date, then the day of the dose of study drug date will be imputed.
  - Otherwise, '01' will be assigned.
- If the time is unknown, then:
  - If the date (day, month, and year) matches the date of the dose of study drug date, then the time of the dose of study drug time will be imputed.
  - Otherwise, '00' will be assigned.
- For partial stop date/time:
  - If the year is unknown, then the date will not be imputed and will be assigned a missing value.
  - If the month is unknown, then 'December' (12) will be assigned.
  - If the day is unknown, then the last day of the month will be assigned.
  - If the time is unknown, then the last time of the day will be assigned.

If time to an event were needed when only the hour, and not the minutes, are reported for the time of the event, then the minutes will be set to zero.

Any deviations from the implementation of the missing date and time algorithms will be documented in the dataset documentation and final report.

12.1. Stratification by Site

The impact of treatment is not expected to vary over site. Unless otherwise indicated, analyses will not be presented by site. Many, if not most, sites are expected to enroll a small number of subjects.

12.2. Unscheduled and/or Repeated Laboratory Results

Unscheduled or repeated laboratory results will be placed together in a separate listing and discussed in a dedicated section of the clinical study report. If any of these values are to replace the values in planned procedures to acquire analysis tables, all such decisions will be justified in the clinical study report.

12.3. Handling of Early Termination Visit Information

Early termination visit data for safety variables will be analyzed at the closest scheduled visit. If the closest visit has valid data, the early termination data will be assigned to the next available visit.

13. CDISC

To meet recent current FDA Guidance (December 2014) on the submission of standardized study data, the study data will be formulated into data sets to provide transparency, traceability, and integrity of trial analysis results from the collection source. Reference is made to FDA Study Data Technical Conformance Guide (March 2015) for adherence to the FDA Guidance[v]. The observed study data will be mapped to the current CDISC Study Data Tabulation Model (SDTM) and serve as the source data from the trial. All study analyses will be completed using analysis data sets that are derived from the SDTM and follow the CDISC Analysis Data Model (ADaM) architecture.

13.1. Clinical Data – CDISC Study Data Tabulation Model (SDTM)

Domains will be mapped to CDISC SDTM using Implementation Guide (IG) version 3.2 or higher. No derived data other than age and converted units of measure that will be analyzed are to be included in the SDTM domains. All SDTM domains will be fully documented with define documents (DEFINE.XML) and a reviewer's guide after database lock and final analyses are completed.

13.2. Analysis Data – CDISC Analysis Data Model (ADaM)

All planned *a priori* and unplanned "post hoc" analyses will be completed using the ADaM data sets derived from the SDTM domains for this study. Analysis data sets will contain all derived study endpoints required for analyses, graphs and specifically designated listings. All analysis data sets will be fully documented with define documents (DEFINE.XML) and a reviewer's guide after database lock and final analyses are completed.

Additional analysis data sets may be developed to support unplanned analyses after database lock. The SAP will not be amended for additional analysis data sets defined for the study and these additional data sets will be documented in the define documentation completed after all analyses are completed for the trial and the clinical study report is written.

14. ADDITIONAL INFORMATION RELEVANT TO THE ANALYSES

14.1. Protocol Deviations

Protocol deviations will be summarized in a listing. Important protocol deviations are defined as deviations that could potentially bias the conclusion. A summary of the number and percentage of subjects with important deviations by deviation category will be provided. A listing of important protocol deviations by subjects and country will also be provided.

14.2. Safety

14.2.1. Concurrent Illness and Medical Conditions

The number and percent of subjects with individual concurrent illness and medical histories will be summarized over all subjects in the safety population. Individual subject listings will also be provided for concurrent illness and medical history. The medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0. A data listing of the body system, verbatim condition/abnormality/procedure, date of onset, and an indicator of continued presence will be provided. A summary table will be provided.

14.2.2. Prior and Concurrent Medications

The number and percent of subjects who took prior and concurrent medications will be summarized descriptively by the ATC class and preferred term as coded in the WHO-Drug dictionary overall subjects. Concomitant medications will be summarized similarly. Prior and concomitant medications will be summarized for the Safety Population. Prior and concomitant medication with the verbatim, ATC level 3 category, preferred term, indication, dosage, route, unit, frequency and start/stop dates of administration will be provided in the listings.

14.3. Subject Enrollment

A summary of subject disposition will display the number of subjects who enrolled, who received study drug, and who remained in the study. Also included in this summary will be the number of subjects who terminated from the study by reason and termination date. Subject enrollment and disposition with reason for termination will be presented in a listing. Reasons for termination (discharge from the study) will also be present in a listing, ordered by primary reason for early termination, then by subject ID.

14.4. Adverse Events

Adverse events (AEs) will be coded using current MedDRA (ex. Version 18.0). Number and percent of subjects reporting AEs will be tabulated for the Safety population. Summaries will be presented by System Organ Class (SOC) and Preferred Term (PT), and further by severity and relationship to the investigational product. In summaries of severity, subjects who reported more than one event that are mapped to the same SOC and/or PT will be counted only once under the strongest severity. In summaries of relationship, subjects who reported more than one event that are mapped to the same SOC and/or PT will be counted only once under each applicable relationship.

All TEAEs will be listed individually by subject. In addition, a separate listing will be produced for AEs that are not treatment-emergent, where appropriate.

14.4.1. Deaths

All deaths, regardless of causality, will be provided in listings and written clinical narratives.

14.4.2. Serious Adverse Events

The number and percent of subjects with Serious Adverse Event (SAE) will be displayed by system organ class and preferred term, and relationship to study medication. Within each preferred term, subjects will be counted only once if they had more than one SAE event reported during the treatment period.

Clinical narratives for each SAE observed will be written to include important data and safety findings related to the individual SAE and included in the final clinical study report.

14.4.3. Adverse Events Leading to Discontinuation of Study Drug Injection

The number and percent of subjects with AE's leading to discontinuation, or interruption, of study drug will be displayed by system organ class and preferred term for each treatment group. Within each preferred term, subjects will be counted only once if they had more than one AE leading to discontinuation, or interruption, of study drug reported during the treatment period.

A listing will be produced for all subjects who reported serious TEAEs or who discontinued study medication due to TEAEs.

14.5. Clinical Laboratory Evaluations

In addition to categorical and continuous descriptive analyses as noted earlier, scatter plots of the baseline value (x-axis) and end of study (y-axis) will be completed for each clinical laboratory parameter. Reference ranges will be highlighted on the plots to identify laboratory assessments that are out of range.

14.6. Physical Examinations

Physical examination results will be listed by subject for baseline and end of study assessment. Changes in physical examination from baseline to end of study will be recorded as adverse events.

15. TABLES, LISTINGS AND FIGURES

Organized listings of data will be provided that show by variable the values for each subject. At the medical writer's direction, listings that show specified variables by subject may be created. Selected details involving the listings are found below. Mock headings that specify the obtained and derived variables that are to be placed in listings will be included with this SAP.

- Inclusion and exclusion criteria will be provided in separate data listing by subject.
- A summary of observed values (all vital sign measurements, bone age, and tanner stage) for each scheduled visit will be presented in the listings.
- Physical examination body system, results (normal, abnormal), date and time of evaluation, clinical significance and a comment describing the abnormality and clinical significance of the abnormality will be in the listings.
- Clinical laboratory test results will be presented in the data listings. Values that are outside of the reference range will be flagged.
- All qualitative pregnancy test results (positive, negative) will be provided with date and study day of collection in the listings.
- All literal and MedDRA adverse events will be in the listings. System organ class, preferred term, severity and relationship to treatment will be presented.

Mock tables that present the analyses planned for this study and mock figures that contain the planned exhibits will be formulated and included with this SAP.

Appendix 5 will be added to this SAP and will contain mock tables, listings and figures.

16. BASELINE VALUES OF DROPPED SUBJECTS

If the study terminates with Part A, subjects not available for primary efficacy evaluation at six months will be compared to available subjects on key baseline parameters as directed by the medical writer. If Part B is invoked, subjects not available for primary efficacy evaluation at 21 months will be compared to available subjects on key baseline parameters as directed by the medical writer.

17. DATA SAFETY MONITORING BOARD

An Independent Data Safety Monitoring Board (DSMB) will be used to a) monitor safety throughout the study and b) determine whether Part B of the study is to be invoked. DSMB

responsibilities will be specified in a DSMB charter. The statistician will prepare data reports as directed in the charter and will be available to the DSMB.

18. CONVENTIONS

Unless otherwise indicated by prevailing considerations, the following conventions will be used.

18.1. Reporting Conventions

- All tables and data listings will be developed in Landscape Orientation, unless presented as part of the text in a CSR.
- Figures will be presented in Landscape Orientation, unless presented as part of the text in a CSR.
- Legends will be used for all figures with more than one variable or item displayed.
- Figures will be presented in color with treatment groups distinguished by different symbols and colors. Lines in figures should be wide enough to view the line after being photocopied.
- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters should be used in tables and data listings. Special characters, such as non-printable control characters, printer specific, or font specific characters, will not be used on a table, figure, or data listing. Hexadecimal character representations are allowed (e.g.,μ,α,β).
- All titles will be centered on a page. The ICH numbering convention is to be used for all tables, figures, and data listings.
- All footnotes will be left justified and the bottom of a page. Footnotes must be present on the page where they are first referenced. Footnotes should be used sparingly and must add value to the table, figure, or data listing. If more than four footnote lines are planned then at the programmer's discretion a cover page may be used to display footnotes.
- Missing values for both numeric and character variables will be presented as blanks in a table or data listing. A zero (0) may be used if appropriate to identify when the frequency of a variable is not observed.
- All date values will be presented as YYYY-MM-DD (e.g., 2013-05-17) ISO 8601 format.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds should only be reported if they were measured as part of the study, also in ISO 8601 format.

- Time durations will be reported in mixed HHh MMm SSs notation (e.g., 5h 32m, or 27h 52m 31s). The use of decimal notation to present (display) time durations should be avoided (e.g. 0.083h = 5m) unless it is necessary to show the computation of time differences in a table, figure, or data listing, in which case both notations may be used to display the time duration.
- All tables, figures, and data listings will have the Table, Listing, or Graph status (DRAFT, FINAL), and a date/time stamp on the bottom of each output.
- All analysis programs developed for a table, figure, or data listing display will be self-contained to facilitate transfer of programs to multiple computing environments and transfer to a regulatory agency (if requested).

18.2. Population Summary Conventions

- Population(s) represented on the tables or data listings will be clearly identified in the last title of the Table as "Population: <name of population>" and will be identical in name to that identified in the protocol or SAP.
- Consistent terminology will be used to define and identify a population.
- Sub-population(s) or special population(s) descriptions will provide sufficient detail to ensure comprehension of the population (e.g., FAS Females, Per-Protocol Males >60 years of age) used for analysis in a table or figure.
- Population sizes may be presented for each treatment or dosing category as totals in the column header as (N=xxxx), where appropriate.
- Population sizes shown with summary statistics are the samples sizes (n) of subjects with non-missing values.
- All population summaries for categorical variables will include all categories that were planned and for which the subjects may have had a response. Percentages corresponding to null categories (cells) will be suppressed.
- All population summaries for continuous variables will include at least N, mean, SD, minimum, and maximum. Other summaries (e.g. number missing, median, quartiles, 5%, 95% intervals, CV or %CV) may be used as appropriate.
- All percentages are rounded and reported to xx.x%. A percentage of 100% will be reported as 100%. Any computation that results in 0% will be reported as 0% unless otherwise indicated.

19. APPENDICES

19.1. Appendix 1: Tanner Stages

Tanner stages[4] are commonly used 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")

19.2. Appendix 2: 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.

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

19.3. Appendix 3: Global Interview Symptom Assessment

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

19.4. Appendix 4: SAP Modifications (TBD)

Change Log			
Version No.	**SAP Date**	**Change / Revision**	**Author(s)**
1.1	06 Jan 2017	Administrative Changes: • Section 6.1.1: Revised language to clarify criteria for adaptive change in design. • Section 6.6: Added "approximately" and "(N ≥ 3)" to clarify actual value equating to 85% of 16 subjects. • Section 7: Added "are the four forms" • Signature Page: Added "Kerlin Lynch, Clinical Trials Manager" to replace "Matt Baldwin, Statistician II"	[redacted] Tolmar), [redacted] (Tolmar)
1.2	02 February 2017	Administrative Changes: • Table 4: removed final column "Distance from P to Limit if P = 0.5" • Section 7: Removed "are the four forms" addition made in version 1.1 for clarity and accuracy. Added "s" to "instance" • Table 5: Moved "X" for Baseline Safety and Safety row under "Categorical Descriptive Analysis" column from "Continuous Descriptive Analysis" column	[redacted] (Tolmar), [redacted] (EMB)
1.3	06 June 2018	Administrative Changes: • Section 8.3.2 – Bullet #4: Removed "/PD" since the analyte is leuprolide. • Section 10.2: Removed "PK/" typo to align definition of ITT to the Protocol. • Footer pages 14-43: Revised page stamp be consistent with pages 1-13 and throughout document. • Signature Page: Added Michael C. Mosier, PhD	[redacted] (Tolmar), [redacted] (Tolmar)

1.4	04 Sep 2018	Administrative Changes: • Section 5.2 – Bullet #5 was Added: "Assess growth velocity of height in cm/year after the first treatment administration." • Section 8.2.2 – Bullet #3 was Added; "The growth velocity of height in cm/year at each available post-baseline measurement. Growth velocity is defined for each visit as (change from Baseline)/[(number of weeks since Baseline)/52)]	[redacted] (EMB)

19.5. Appendix 5: Mock Tables, Listings and Figures (TBD)

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

STATISTICAL ANALYSIS PLAN APPROVAL

SIGNATURES

[redacted]
Printed Name

[redacted]
Signature

Vice President, Clinical Development, TOLMAR Inc.
Title

14/Sept/2018
Date

[redacted]
Printed Name

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Clinical Trials Manager, TOLMAR Inc.
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14 SEP 2018
Date

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Managing Member, Summit Analytical
Title

19 Sept 2018
Date

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Printed Name

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Signature

Director, Biostatistics
EMB Statistical Solutions, LLC
Title

20 Sep 2018
Date

End Notes

[i] US Federal Register. International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.
[ii] American Statistical Association. Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, August 7, 1999. http://www.amstat.org/about/ethicalguidelines.cfm
[iii] Royal Statistical Society. The Royal Statistical Society: Code of Conduct, August 1993. http://www rss.org.uk
[iv] Marshall WA and Tanner JM. Variations in Pattern of Pubertal Changes in Girls. 1969; 44:291-303.
[v] Office of Communications, Division of Drug Information Center for Drug Evaluation and Research, Food and Drug Administration 10001 New Hampshire Ave., Hillandale Bldg., 4th Floor Silver Spring, MD 20993 Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353 Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm Guidance for Industry *Providing Regulatory Submissions In Electronic Format – Standardized Study Data.* December 2014.