AN OPEN-LABEL, SINGLE-ARM STUDY OF THE EFFICACY, SAFETY AND PHARMACOKINETIC BEHAVIOR OF LEUPROLIDE MESYLATE INJECTABLE SUSPENSION (LMIS 25 MG) IN SUBJECTS WITH PROSTATE CANCER

Protocol No.: FP01C-17-001 (NCT03261999)

STATISTICAL ANALYSIS PLAN

Version: 1.1

Date: 05-Dec-2018

Biostatistician:

Confidentiality Statement

Approval of Statistical Analysis Plan
Protocol No : FP01C-17-001

The undersigned approved the SAP Version 1.1, dated 05-Dec-2018 as final.

Programming of the tables, figures and listings based upon the specifications within this document can proceed.

Foresee Pharmaceuticals Co., Ltd Approval:

███████████	██████	Dec 4, 2018 PST
Signature (Title: SVP and Head of Development	Print Name	**Date**

QPS-Qualitix Approval:

████████████	██████████	06Dec2018
Signature (Director of BDM)	Print Name	**Date**

<u>Please Note:</u>

QPS-Qualitix will not notify Foresee Pharmaceuticals Co., Ltd of minor modifications (e.g. modification of column or title) of tables, listings or figures that are different from SAP when generating data-driven tables, listings or figures after database lock.

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LIST OF ABBREVIATIONS AND TERMS

TERM	DEFINITION
AE(s)	Adverse Event(s)
AIC	Akaike's information criteria
ALT (SGPT)	Alanine Aminotransferase
ALP	Alkaline Phosphatase
AST (SGOT)	Aspartate Transaminase
BDM	Biostatistics & Data Management
BLQ	below the limit of quantitation
BP	Blood Pressure
BT	Body Temperature
BUN	Blood Urea Nitrogen
Ca	Calcium
CBC	Complete Blood Count
CI	Confidence Interval
CRF	Case Report Form
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
ENT	Ear, Nose, and Throat
ET	Early Termination
EOS	End of Study
FDA	Food and Drug Administration
Hb	Hemoglobin
Hct	Hematocrit
HDL	High Density Lipoprotein
HR	Heart Rate
IP	Investigational Product
I-PSS	International Prostate Symptom Score

TERM	DEFINITION
IS	Internal Standard
ITT	Intent-to Treat
K	Potassium
LC/MS/MS	Liquid Chromatography-tandem Mass Spectrometry
LDL	Low Density Lipoprotein
LH	Luteinizing Hormone
LLOQ	lower limit of quantitation
LMIS	Leuprolide Mesylate Injectable Suspension
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Magnesium
msec	milliseconds
Na	Sodium
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per-Protocol
PR	Partial Response
PS	Performance Status
PSA	Prostate Specific Antigen
QTcF	QT interval corrected by Fridericia's Formula
RBC	Red Blood Cell
RR	Respiratory Rate
SAE(s)	Serious Adverse Event(s)
S_{Cr}	Serum Creatinine
Scrn	Screening
SOC	System Organ Class
SOP	Standard Operation Procedure
TEAE	Treat emergent adverse event

TERM	DEFINITION
VAS	Visual Analogue Scale
WBC	White Blood Cell
WHO	World Health Organization

1. INTRODUCTION

This is a multi-national, multi-center, open-label, single-arm and phase III study to determine the efficacy, safety, and pharmacokinetic profile of LMIS 25 mg in patients with prostate cancer. Approximately 133 subjects will be enrolled in this study.

This statistical analysis plan (SAP) is based on protocol version 1.1, dated 20-Nov-2017. The SAP provides details of data handling procedures and statistical analysis methods for efficacy and safety evaluations. It also outlines statistical programming specifications for tables, listings and figures, and other details on the analyses not provided in the study protocol. It is noted that in case there is discrepancy between the SAP and the protocol then the SAP will supersede the protocol.

This SAP will include efficacy and safety analysis only. The pharmacokinetic (PK) analysis plan is not part of this SAP.

2. STUDY OBJECTIVE

Primary objectives

The primary objective of this study is to assess the efficacy and safety of LMIS 25 mg for up to 24 weeks following 2 subcutaneous doses given 12 weeks apart in subjects with prostate cancer

Secondary objectives

To establish the serum PK profile of leuprolide for LMIS 25 mg in a subset of subjects with prostate cancer

To assess the ECG effects of leuprolide in relationship to plasma concentrations of both leuprolide and testosterone

3. STUDY DESIGN

3.1 Overall Study Design

This is a multi-national, multi-center, open-label, single-arm study. All subjects will be males with prostate cancer judged to be candidates for medical androgen ablation therapy and all will receive LMIS 25 mg in an unblinded fashion. Subjects with morning serum testosterone level > 150 ng/dL at screening, adequate organ functions, ECOG performance score ≤ 2, and have a life expectancy of at least 18 months will be eligible to enter the study.

The study duration is approximately 24 weeks. Two separate doses of LMIS 25 mg will be given to subjects by subcutaneous injection at 12 weeks apart in an unblinded manner. LMIS 25 mg will be administered on Day 0 (Visit 2) and Day 84 (Visit 13). At the end of 12 weeks (Day 84), all

subjects who have tolerated LMIS 25 mg will be administered the second dose of LMIS 25 mg and will be followed for tolerability, safety, efficacy, PK/PD parameters for another 12 weeks (Day 168/week 24).

To evaluate the sustained castration testosterone level after two doses of LMIS 25 mg injections, the first enrolled 30 subjects are considered as a subset for PK assessment and will be followed for an additional 2 weeks (Day 182/week 26) post Day 168 (week 24) to establish the extended pharmacokinetic and pharmacodynamics profiles of serum leuprolide and testosterone levels. This additional sampling is meant to assess the flexibility of the time period between doses during routine use of LMIS 25 mg.

The efficacy assessments will be performed in both ITT and PP populations. Efficacy assessment will include the percentage of subjects reached the castrate levels ($\leq$ 50 ng/dL) of serum testosterone on Day 28 (week 4) post the first dosing of LMIS 25 mg, the effect of LMIS 25 mg on serum levels of testosterone, PSA, and luteinizing hormone (LH). The acute-on-chronic (surge) effect of serum testosterone and LH will also be monitored in all subjects. In addition, the effects of LMIS 25 mg on the percentage of subject with PSA relapse and on the percentage of subjects that achieves normal serum PSA level will be determined at the end of study.

Safety assessments will include AE/SAE monitoring. All AEs and SAEs that occur during the study period will be recorded in Case Report Forms (CRFs) and followed until resolution or until the events are considered stable. In addition, SAEs will be recorded and reported as required by both local and international regulatory requirements.

Additional safety assessments include vital signs, physical examinations, local injection site reaction, assessments of bone pain, urinary signs, and symptoms, and laboratory assessments.

All concomitant medication used during the study period will be recorded in the CRF until the end of the study.

The remaining approximately 103 subjects will have blood samples collected for determining the serum leuprolide on Day 0 (prior to the first dose of LMIS 25 mg, and 4 hours post the first dose), Days 1, 3, 14, 21, 28, 56, 77, 84 (week12: prior to the second dose and 4 hours post dose), 85, 86, 87, 98, 112, 140, 161, and 168 (week 24/end of study (EOS)).

Serum testosterone and LH levels will be determined in all subjects using blood samples collected at the specified time points along with serum leuprolide analysis.

Blood samples for determining the extended PK/PD profile of serum testosterone concentrations will be collected in the first enrolled 30 subjects on Day 0 (prior to the first dose of LMIS 25 mg and 2 h, 4 h, and 8 h post dose), Days 1, 2, 3, 7, 14, 21, 28, 42, 56, 77, 84 (week 12: prior to the second dose and 2 h, 4 h, and 8 h post dose), Days 85, 86, 87, 98, 112, 126, 140, 161, 168 (week 24) and Day 182 (week 26).

For determining the serum testosterone concentration in the remaining 103 subjects, blood samples will be collected on Day 0 (prior to the first dose of LMIS 25 mg and 4 hours post dose), Days 1, 3, 14, 21, 28, 56, 77, 84 (week 12: prior to the second dose of LMIS 25 mg and 4 hours post dose), 85, 86, 87, 98, 112, 140, 161, and 168 (week 24/end of study (EOS)).

Blood samples for determining the serum LH concentrations will be collected on Day 0 (prior to the first dose of LMIS 25 mg), Days 1, 2, 3, 7, 14, 21, 28, 42, 56, 77, 84 (week 12, prior to the second dose of LMIS 25 mg), 85, 86, 87, 98, 112, 126, 140, 161, 168 (week 24; end of study) in the first enrolled 30 subjects.

For determining the serum LH concentration in the remaining 103 subjects, blood samples will be collected on Day 0 (prior to the first dose of LMIS 25 mg), Days 1, 3, 14, 21, 28, 56, 77, 84 (week 12: prior to the second dose of LMIS 25 mg), 85, 86, 87, 98, 112, 140, 161, and 168 (week 24/end of study (EOS)).

Serum testosterone concentrations will be measured using a validated LC/MS/MS method. The method validation follows the European Medicines Agency (EMA) Guideline on Bioanalytical Method Validation (EMEA/CHMP/EWP/192217/2009) and the FDA Guidance for Industry: Bioanalytical Method Validation, May 2001.

The measurement of serum LH concentrations will be performed using a validated bioanalytical assay following the FDA and ICH guidance..

For subjects who terminate early or withdraw, phone contacts will be performed at 12 weeks after the last injection of the investigational product (IP) to collect information concerning drug-related AEs, concomitant medication, non-drug therapy received for AE treatment, disease progression status, and subject survival status.

Table 3.1-1   Study Schedule Visits 1-13

	Scrn	1st Dose				Follow Up										2nd Dose			
Visit	1	2				3	4	5	6	7	8	9	10	11	12	13			
Week		1				1	1	1	1	2	3	4	6	8	11	12	12	12	12
Day	-28 to -1	0				1	2	3	7	14	21	28	42#	56	77	84*			
Hour		0	2	4	8											0	2	4	8
Informed consent	X																		
Inclusion/Exclusion criteria	X																		
Subject screening number	X																		
Subject enrollment number		X																		
Demographics	X																		
Tumor history[1]/Medical and medication history[2]/comorbidity	X																		
Concomitant treatments[2]	X	X	X	X	X	X	X	X	X	X	X	X	X#	X	X	X	X	X	X
Physical examination[3]	X															X			
Vital signs[4]	X	X				X	X	X	X	X	X	X	X#	X	X	X			
ECOG PS	X	X																	
12-lead ECG[5]	X	X		X5								X				X		X5	
Study treatment		X														X			
Local injection site reaction			X	X	X	X	X										X	X	X
Adverse event/SAE	X	X	X	X	X	X	X	X	X	X	X	X	X#	X	X	X	X	X	X
Hormone level																			
Testosterone[6]	X	X	X#	X	X#	X	X#	X	X#	X	X	X	X#	X	X	X	X#	X	X#
Luteinizing hormone7	X	X				X	X#	X	X#	X	X	X	X#	X	X	X			
Lab chemistry																			

	Scrn	1st Dose				Follow Up										2nd Dose			
Visit	1	2				3	4	5	6	7	8	9	10	11	12	13			
Week		1				1	1	1	1	2	3	4	6	8	11	12	12	12	12
Day	-28 to -1	0				1	2	3	7	14	21	28	42#	56	77	84*			
Hour		0	2	4	8											0	2	4	8
Hematology[8]/ Biochemistry[9]	X/X	X/X								X/X		X/X				X/X			
Pharmacokinetic serum sample for leuprolide mesylate (LM)		X	X#	X	X#	X	X#	X	X#	X	X	X	X#	X	X	X	X#	X	X#
PSA	X	X										X				X			
Urinalysis[10]	X	X								X		X				X			
HbA1c	X																		
Bone pain (VAS)/ Urinary signs and symptoms (I-PSS)		X/X				X/X			X/X	X/X		X/X		X/X		X/X			

Abbreviation: Baseline: Day 0; AE: Adverse Event; BT: Body temperature; ECG: Electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group Scale of Performance Status; EOS: end of study; ET: early termination; HbA1c: glycosylated hemoglobin; HR: Heart rate; LH: luteinizing hormone; PD: Pharmacodynamic(s); PK: Pharmacokinetic(s); PSA: Prostate Specific Antigen; RR: Respiratory rate; Scrn: Screening. BP: Blood pressure; VAS: Visual Analogue Scale; I-PSS International Prostate Symptom Score

*   If the subject cannot return on Day 84 (the second dose, Visit 13), please have the subsequent visits on Days 85, 86, 87, 98, and 112 to be scheduled according to the actual occurred date of the Day 84 visit. For the Day140 Visit (Visit 20), adjust the scheduled date according to the date when the first injection was received.

Procedures/ examinations for the first enrolled 30 subjects only.

[1]   Cancer/tumor history should be recorded in a life-time basis.

[2]   Medical and medication history (including procedural and surgical history, blood donations, and vaccinations) will be recorded up to 6 months prior to screening Visit. Concomitant medication use will be recorded up to 6 months prior to screening visit.

[3] Height will be only measured at screening visit. Weight will be measured at screening, Day 84, and EOS.

[4] Vital signs include BP, HR, RR, and BT.

[5] 12-lead ECG monitoring will be performed at specified time points. When 12-lead ECG has to be performed on dosing days, it will be performed prior dosing and at 4-hour post LMIS 25 mg injection in all subjects on dosing days (Days 0 and Day 84).

[6] Testosterone samples will be collected in the morning at specified time points as shown in the above schedule. On dosing days (Day 0 and Day 84), blood samples for testosterone analysis will be collected before LMIS 25 mg administration. Serum testosterone levels will be analyzed at the QPS Bioanalytical Lab. For fast turn-around of assay results, a sample for the screening testosterone will also be sent to the Central Lab. After that, additional samples for testosterone may be ordered by the investigator at their discretions and analyzed at the Central Lab using commercial diagnostic assays for fast turn-around of results.

[7] LH samples will be collected in the morning at specified time points as shown in the above schedule. On dosing days (Day 0 and Day 84), blood samples for LH analysis will be collected before LMIS 25 mg administration. Serum samples for LH concentrations will be analyzed at the QPS Bioanalytical Lab using a validated ELSIA method. More frequent tests of LH may be ordered by the investigators at their discretion, and these samples can be analyzed at the Central Lab for a faster data turn-around. Serum samples to the QPS Bioanalytical Lab will be batched and shipped periodically.

[8] Hematology tests include CBC, Hb, Hct, RBC count, WBC count with differential and platelet count.

[9] Biochemistry tests include ALT, AST, ALP, total bilirubin, BUN, Serum Cr, electrolytes (K, Na, Mg, Ca and P), blood glucose, and lipid profile (LDL, HDL, triglycerides)

[10] Urinalysis tests include pH, specific gravity, leukocyte, erythrocyte, urine glucose, nitrate, and protein.

Note: Regarding the time window for blood sample collection, at 2, 4, 8 hours post LMIS 25 mg administration on Day 0 (Visit 1) and Day 84 (Visit 13), a 15-minute time window is allowed; at Visits 6 to 9 (Day 7 to Day 28), a ± 1-day window is allowed. At Visits 10 and 12 (Day 42 to Day 77), a ± 3-day window is allowed. At Visits 13 to 16 (Day 84, for the second dose injection, week 12, to Day 87), only ± 1-day window is allowed. At Visits 17 to 21 (Day 98 to Day 161), a ± 3-day window is allowed. At Visits 22 (Day 168), a ± 5-day window is allowed. At Visit 23 (Day 182), a ± 3-day window is allowed.

Table 3.1-2   Study Schedule Visits 14-EOS

	Follow Up								EOS/ET[+]	PK-extended Follow up
Visit	14	15	16	17	18	19	20	21	22	23#
Week	13	13	13	14	16	18	20	23	24	26
Day	85*	86*	87*	98*	112*	126#	140	161	168	182#
Concomitant treatments[2]	X	X	X	X	X	X#	X	X	X	X#
Physical examination[3]									X	
Vital signs[4]	X	X	X	X	X	X#	X	X	X	X#
ECOG PS										
12-lead ECG[5]									X	
Study treatment										
Local injection site reaction	X	X								
Adverse event/SAE	X	X	X	X	X	X#	X	X	X	X#
Hormone level										
Testosterone[6]	X	X	X	X	X	X#	X	X	X	X#
Luteinizing hormone[7]	X	X	X	X	X	X#	X	X	X	
Lab chemistry										
Hematology[8]/ Biochemistry[9]									X/X	
Pharmacokinetic serum sample for leuprolide mesylate (LM)	X	X	X	X	X	X#	X	X	X	X#
PSA									X	
Urinalysis[10]									X	
HbA1c									X	
Bone pain (VAS)/ Urinary signs and symptoms (I-PSS)					X/X		X/X		X/X	

Abbreviation: Baseline: Day 0; AE: Adverse Event; BT: Body temperature; ECG: Electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group Scale of Performance Status; EOS: end of study; ET: early termination; HbA1c: glycosylated hemoglobin; HR: Heart rate; LH: luteinizing hormone; PD: Pharmacodynamic(s); PK: Pharmacokinetic(s); PSA: Prostate Specific Antigen; RR: Respiratory rate; Scrn: Screening. BP: Blood pressure; VAS: Visual Analogue Scale; I-PSS: International Prostate Symptom Score.

* If the subject cannot return on Day 84 (the second dose, Visit 13), please have the subsequent visits on Days 85, 86, 87, 98, and 112 to be postponed according to the actual occurred date of the Day 84 visit. For the Day140 Visit (Visit 20), adjust the scheduled date according to the date when the first injection was received.

Procedures/ examinations for the first enrolled 30 subjects only.

+ For early termination subjects (ET), end of study (EOS) procedure and examination should be performed on that day. In addition, phone contacts should be performed at 12 weeks after the last injection of investigational product to collect drug-related AE, concomitant medication or non-drug therapy received for AE treatment, disease progression status, and subject survival status.

[2] Concomitant medication use will be recorded up to 6 months prior to screening visit.

[3] Height will be only measured at screening visit. Weight will be measured at screening, Day 84 (week 12), and EOS (Week 24).

[4] Vital signs include BP, HR, RR, and BT

[5] 12-lead ECG monitoring will be performed at specified time points.

[6] Testosterone samples will be collected in the morning at specified time points as shown in the above schedule. Serum testosterone levels will be analyzed at the QPS Bioanalytical Lab.

[7] LH samples will be collected in the morning at specified time points as shown in the above schedule. On dosing days (Day 0 and Day 84), blood samples for LH analysis will be collected before LMIS 25 mg administration. Serum samples for LH concentrations will be analyzed at the QPS Bioanalytical Lab using a validated ELSIA method. More frequent tests of LH may be ordered by the investigators at their discretion, and these samples can be analyzed at the Central Lab for a faster data turn-around. Serum samples to the QPS Bioanalytical Lab will be batched and shipped periodically.

[8] Hematology tests include CBC, Hb, Hct, RBC count, WBC count with differential and platelet count.

[9] Biochemistry tests include ALT, AST, ALP, total bilirubin, BUN, Serum Cr, electrolytes (K, Na, Mg, Ca and P), blood glucose, and lipid profile (LDL, HDL, triglycerides)

[10] Urinalysis tests include pH, specific gravity, leukocyte, erythrocyte, protein, urine glucose, and nitrate.

Note: Regarding the time window for blood sample collection, at 2, 4, 8 hours post LMIS 25 mg administration on Day 0 (Visit 1) and Day 84 (Visit 13), 15-minute time window is allowed; at Visits 6 to 9 (Day 7 to Day 28), a ± 1-day window is allowed. At Visits 10 and 12 (Day 42 to Day 77; week 6 to week 11), a ± 3-day window is allowed. At Visits 13 to 16 (Day 84 for the second dose injection, week 12 visit, to Day 87), only ± 1-day window is allowed. At Visits 17 to 21 (Day 98 to Day 161), a ± 3-day window is allowed. At Visits 22 (Day 168), a ± 5-day window is allowed. At Visit 23 (Day 182), a ± 3-day window is allowed.

3.2 Primary Endpoint

The primary endpoint of efficacy is to determine the percentage of subjects with a serum testosterone concentration suppressed to castrate levels ($\leq$ 50 ng/dL) on Day 28 $\pm$ 1 day (week 4) following the first injection of LMIS 25 mg, and the proportion of subjects with serum testosterone suppression ($\leq$ 50 ng/dL) from Day 28 $\pm$ 1 day (week 4) through Day 168 $\pm$ 5 days (week 24) until the end of the study.

3.3 Secondary Endpoint

Efficacy:

- The mean acute-on-chronic (surge) changes in testosterone and LH levels from just prior to the second injection through 14 days after the second injection of LMIS 25 mg (Days 85-87, week 13; Day 98 [14 days post the second dose], week 14)

- Effect of LMIS 25 mg on change of serum prostate-specific antigen (PSA) levels

- Effect of LMIS 25 mg on change of serum LH levels

- The percentage of subject with PSA relapse defined as after achieving the serum PSA level $\leq$ 4 ng/mL post LMIS 25 mg injection but with an increase in serum PSA of >50% PSA nadir by Day 168 (week 24)

- The percentage of subject achieving normal serum PSA level (<4 ng/mL) on Day 168 $\pm$ 5 days (week 24)

- The percentage of subjects with enhanced serum testosterone concentration suppression to $\leq$ 20 ng/dL on Day 28 $\pm$ 1 day (week 4) and on Day 168 $\pm$ 5 days (week 24)

Safety:

- Adverse event (AE)/ serious adverse event (SAE) reporting

- Assessment of injection site reaction

- Change in bone pain measurement (by Visual Analogue Scale [VAS] scale)

- Change in urinary signs and symptoms and total scores (by the International Prostate Symptom Score, I-PSS sheet)

- Change in vital signs (BP, HR, RR, weight)

- Change in physical examinations with clinical significance compared to baseline by principal investigator's judgment

- Change in lab data, including liver function (AST, ALT, ALP), renal function (BUN, SCr), complete blood count with platelets, clinical chemistries (K, Na, Mg, Ca and P), urinalysis, serum glucose, lipid profile (LDL, HDL, triglycerides), and HbA1c level

- Clinically significant changes in 12-lead resting electrocardiogram (ECG) per the investigator's judgment

- Change from baseline in the ECG parameters of QTcF, HR, PR, and QRS

- Change from baseline in the ECG parameters of QTcF, HR, PR, and QRS in relation to the serum concentrations of leuprolide and testosterone

3.4 Study Population

Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Males aged $\geq$ 18 years old

2. Males with histologically confirmed cancer of the prostate

3. Subjects who are judged by the attending physician and/or principal investigator to be a candidate for androgen ablation therapy

4. Baseline morning serum testosterone level > 150 ng/dL performed at screening visit

5. Eastern Cooperative Oncology Group (ECOG) Performance score $\leq$ 2

6. Life expectancy of at least 18 months

7. Laboratory values

   - Absolute neutrophil count $\geq$ 1,500 cells/μL

   - Platelets $\geq$ 100,000 cells/μL

   - Hemoglobin $\geq$ 10 gm/dL

   - Total bilirubin $\leq$ 1.5 $\times$ upper limit of normal (ULN)

   - AST (SGOT) $\leq$ 2.5 $\times$ ULN

   - ALT (SGPT) $\leq$ 2.5 $\times$ ULN

   - Serum creatinine $\leq$ 1.5 mg/dL

   - Lipid profile within acceptable range according to investigator's opinion

- Serum glucose within acceptable range according to investigator's opinion

- HbA1c ≤9.5%

- Clinical chemistries (K, Na, Mg, Ca and P) within acceptable range according to investigator's opinion

- Normal urinalysis results within:

  ✓ RBCs ≤ 3 RBCs/hpf

  ✓ WBCs ≤ 5 WBCs/hpf

  ✓ Nitrate: negative

  ✓ Glucose: <0.1g/dL; but <1.0 g/dL in subjects with diabetes mellitus

8. Agree to use male contraceptive methods during study trial

9. In the investigator's opinion, the ability to understand the nature of the study and any hazards of participation, and to communicate satisfactorily with the investigator and to participate in, and to comply with, the requirements of the entire protocol

10. All aspects of the protocol explained and written informed consent obtained

Exclusion Criteria

Subjects presenting with any of the following will not be included in the present study.

1. Receipt of chemotherapy, immunotherapy, cryotherapy, radiotherapy, or anti-androgen therapy concomitantly, or within 8 weeks prior to screening visit, for treatment of Cancer of the prostate. Radiation for pain control will be allowed during the study.

2. Receipt of any vaccination (including influenza) within 4 weeks of screening visit

3. History of blood donation within 2 months of screening visit

4. History of anaphylaxis to any LH-RH analogues

5. Receipt of any LH-RH suppressive therapy within 6 months of screening visit

6. Patients who were previously enrolled in the LMIS 50 mg study

7. Major surgery, including any prostatic surgery, within 4 weeks of screening visit

8. History and concomitant clinical and radiographic evidence of central nervous system/spinal cord metastases and subjects at risk for spinal cord compression

9. Clinical evidence of active urinary tract obstruction and subjects at risk for urinary obstruction

10. History of bilateral orchiectomy, adrenalectomy, or hypophysectomy

11. History or presence of hypogonadism, or receipt of exogenous testosterone supplementation within 6 months of screening visit

12. Clinically significant abnormal ECG and/or history of clinically significant cardiovascular disease as judged by the investigator

13. History of drug and/or alcohol abuse within 6 months of screening visit

14. Contraindication to leuprolide or an LH-RH agonist as indicated on package labeling

15. Use of 5-alpha reductase inhibitor within the last 6 months of screening visit

16. History or presence of insulin-dependent diabetes mellitus (Type I). Presence of well controlled diabetes mellitus Type II will be allowed if only oral hypoglycemic are required. Prostate cancer subjects with poor controlled diabetes mellitus with Hb1Ac > 9.5% or urine glycosuria > 1.0 g/dL should be excluded.

17. Use of systemic corticosteroids at a dose > 10 mg/d or anti-androgens

18. Use of any investigational agent within 4 weeks of screening visit

19. Use of any over-the-counter (OTC) medication within 4 weeks of screening visit except for those listed in the permitted Concomitant Treatment section.

20. Uncontrolled intercurrent illness that would jeopardize the subject's safety, interfere with the objectives of the protocol, or limit the subject's compliance with study requirements, as determined by the investigator in consultation with the sponsor

4. GENERAL STATISTICAL ISSUES

For data listings, all raw data will be displayed exactly as provided. Partial date(s) will be listed as provided in the listings. The partial date(s) will be imputed when using for calculation. For the start date, a missing month is supplied a default value of January and a missing day is supplied a default value of 1. For the stop date, a missing month is supplied a default value of December and a missing day is supplied a default value of the last day of the month. The Baseline is defined as the last observation prior to first dose unless otherwise specified.

4.1 Continuous endpoints

Continuous variables will be summarized and presented as number of observations, mean, standard deviation (SD), median, range, Hodges-Lehmann estimator, and 95% CI. Changes from baseline

will be tested by paired t-test or Wilcoxon signed-rank (if data violated the normal assumption, i.e. the p-value of test of normality is <0.05) test for continuous variables using a significance level of 0.05. For summaries of quantitative data, the median, minimum and maximum value will be reported exactly as the raw data are reported; measures of central tendency (means will be reported as one decimal more than the raw data and measure of variance (SD) will be reported as the two decimals more than the raw data.

4.2 Categorical endpoints

Categorical variables will be presented by frequency and percentage.

4.3 Time-to-event endpoints

The time-to-event endpoint, percentage of subjects with testosterone suppression ($\leq$ 50 ng/dL) from Day 28 (week 4) through Day 168 $\pm$ 5 days (week 24) will be analyzed by Kaplan-Meier method. The event is defined as as occurring in subjects with a testosterone level > 50 ng/dL between Day 28 (week 4) and Day 168 (week 24), and it will be presented as number of subjects with event (event number), percentage of subjects with event, suppression rate by day 168 along with 95% confidence interval, mean, median and 95% confidence interval for median. Some situations are noted for efficacy analysis by Kaplan-Meier method:

1. The subject has an event and it will be analyzed as an event on the day of first testosterone escape.

2. The subject with more than one missing testosterone value will be censored on day of last measurement.

3. Any subject having more than one missing testosterone values will be censored on the day of last measurement before the first missing testosterone measurement.

4. If subject does not have serum testosterone suppression to castrate level (i.e. serum testosterone levels > 50 ng/dL) by Day 28 (week 4), the event date will be set as Day 28 for the analysis of percentage of subjects with testosterone suppression ($\leq$ 50 ng/dL) from Day 28 (week 4) through Day 168 (week 24).

4.4 Sample size estimation and power

Approximately 133 subjects are expected to be enrolled in this study. A sample size of 120 will achieve 85% power to detect a difference (P1-P0) of 0.0700 by using a one-sided binomial test. The

target significance level is 0.0250. This assumes that the population proportion under the null hypothesis is 0.9000 and under the alternative to be 0.97. The estimated drop-out rate is 10%, so approximately 13 subjects may drop out from the study before Day 168 (week 24).

Currently, there are totally 144 subjects enrolled in this study.

5. DATA HANDLING PROCEDURES

5.1 Coding System

All AEs will be coded according to the MedDRA dictionary, version 21.0 or higher, and be reported by System Organ Class and Preferred Term.

Concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary.

5.2 Missing Data Handling

For missing data related to a safety or efficacy endpoints, no missing data imputation method will be performed unless otherwise specified.

6. ANALYSIS OF STUDY POPULATIONS

In this study, there will be five populations, including intention-to treat (ITT), per protocol (PP), safety, ECG, and PK/ECG populations. The ITT and PP populations will be used for the efficacy analysis. The safety population will only be used for the safety analysis. The ECG and PK/ECG populations will be used for the ECG analysis. The populations for analysis applied in this study are defined as follows:

6.1 Intent-to-treat (ITT) Population

The Intention-To-Treat (ITT) population will consist of any subject receiving at least one dose of LMIS 25 mg.

6.2 Per-protocol (PP) Population

The Per Protocol (PP) population will be composed of those subjects who received 2 doses of LMIS 25 mg without major deviations that will impact the assessment of the primary efficacy endpoint.

6.3 Safety Population

The safety population will consist of any subject receiving a dose of LMIS 25 mg.

6.4 Electrocardiogram (ECG) Population

The ECG population will consist of any subject receiving at least one dose of LMIS 25 mg and who had an ECG value measured for at least 1 post dose time point.

6.5 Pharmacokinetic/Electrocardiogram (PK/ECG) Population

The PK/ECG population will consist of any subject in the ECG population with post dose time-matched serum concentrations of leuprolide or testosterone.

The analysis of study population will be summarized in Table 14.1.1. Besides, subjects excluded from the analysis will be listed in Listing 16.2.3.

7. DISPOSITION OF PATIENTS AND STUDY COMPLETION

Data on the study completion status and primary reason for study discontinuation will be listed in Listing 16.2.1. All subjects' disposition and completion status will be summarized in Table 14.1.1. Individual subject eligibility will be listed in Listing 16.2.2.1. All protocol deviation(s) will be listed in Listing 16.2.2.2.

8. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographics information (Age (years), Gender, Race and Ethnicity) will be listed in Listing 16.2.4.1. Demographics information and baseline characteristics included: Age (years), Gender, Race, Ethnicity, Diagnosis (days) of prostate carcinoma history, each TNM of prostate carcinoma history and ECOG performance will be summarized in Table 14.1.2.

8.1 Tumor History and Medical History

Medical history and concurrent medical conditions data will be listed by subject as following:
Listing 16.2.4.2: Tumor History
Listing 16.2.4.3: Other Tumor History
Listing 16.2.4.4: Previous Treatment of Malignant Disease
Listing 16.2.4.5: Medical/ Surgery History

Listing 16.2.4.6: Previous Blood Donation

9. EFFICACY ANALYSIS

9.1 Primary Efficacy Variable

The primary endpoint of efficacy is to determine the percentage of subjects with a serum testosterone concentration suppressed to castrate levels ($\leq$ 50 ng/dL) on Day 28 $\pm$ 1 day (week 4) following the first injection of LMIS 25 mg and to determine the proportion of subjects with serum testosterone suppression ($\leq$ 50 ng/dL) from Day 28 $\pm$ 1 day (week 4) through Day 168$\pm$ 5 days (week 24) until the end of the study.

The percentage of subjects with a serum testosterone concentration suppressed to castrate levels ($\leq$ 50 ng/dL) on Day 28 $\pm$ 1 day (week 4) and on Day 168$\pm$ 5 days (week 24) will be analyzed using a standard large sample normal approximation to a Binomial distribution and it will be summarized as count, percentage and exact 95% CI for binomial proportion.

The percentage of subjects with testosterone suppression ($\leq$ 50 ng/dL) from Day 28 (week 4) through Day 168 $\pm$ 5 days (week 24) will be analyzed using the Kaplan-Meier approach. In this analysis an event is defined as occurring in subjects with a testosterone level > 50 ng/dL between Day 28 (week 4) and Day 168 (week 24). To accommodate drop-out and missing values the following censoring rules will be observed:

Table 9.1-1   Data Censoring Rules

| Subject Discontinued | Day 28- 168 or Day of Discontinuation | | To Be Handled As |
	More Than 1 Missing Testosterone Value	Any Escape*	
Yes	No	No	Censored on day of last measurement
Yes	No	Yes	Event on day of first escape
Yes	Yes	No	Censored on day of last measurement before the first missing

Yes	Yes	Yes	Event on day of first escape
No	No	No	Censored on Day 168
No	No	Yes	Event on day of first escape
No	Yes	No	Censored on day of last measurement before the first missing
No	Yes	Yes	Event on day of first escape
No suppression by Day 28			Event on Day 28

*The escape (event) is defined as subject with a testosterone level >50 ng/dL

The testosterone level will be listed by subject and visit in Listing 16.2.6.1.

The duration of time to reach a serum testosterone of >50 ng/dL is calculated from Day 28 to Day 168 or Day of Discontinuation. The duration of time to reach a serum testosterone of >50 ng/dL will be summarized and presented as number of subjects with event (event number), percentage of subjects with event, suppression rate by day 168 along with 95% confidence interval, mean, median and 95% confidence interval for median. A positive outcome to the study will be achieved if the lower 95% confidence interval bound for the response rate at Day 168 is greater than 90%.

Subjects exhibiting post-suppression breakthrough of serum testosterone to >50 ng/dL will also be summarized based on a subset for subjects who reach castration on day 28. The calculation formula is: [The subjects exhibiting post-suppression excursions of serum testosterone to >50 ng/dL at specific visit] / [The total number of subjects who reach castration at day 28 and has nonmissing serum testosterone value at specific visit] x 100%. It will be summarized as count, percentage and exact 95% CI for binomial proportion.

The summary of primary efficacy analysis will be presented as following:
Table 14.2.1: Summary of Subjects with a Serum Testosterone Concentration Suppressed to Castrate Levels (ITT Population)
Table 14.2.2: Summary of Subjects with Serum Testosterone Suppression Maintained from Day 28 through Day 168 (ITT Population)
Table 14.2.3: Summary of Subjects Exhibiting Post-Suppression Breakthrough of Serum Testosterone to >50 ng/dL (ITT Population)

Table 14.2.13: Summary of Subjects with a Serum Testosterone Concentration Suppressed to Castrate Levels (PP Population)

Table 14.2.14: Summary of Subjects with Serum Testosterone Suppression Maintained from Day 28 through Day 168 (PP Population)

Table 14.2.15: Summary of Subjects Exhibiting Post-Suppression Breakthrough of Serum Testosterone to >50 ng/dL (PP Population)

Also, the Kaplan-Meier curve for duration of time to reach a serum testosterone of >50 ng/dL will be presented in Figure 14.2.1 and Figure 14.2.2 for ITT and PP populations.

9.2 Secondary Efficacy Variables

The analyses of secondary endpoints will be based on the following

- The mean acute-on-chronic (surge) changes in testosterone and LH levels from just prior to the second injection through 14 days after the second injection of LMIS 25 mg (Days 85-87, week 13; Day 98 [14 days post the second dose], week 14)

An 'acute-on-chronic' change is defined as a >25% increase in testosterone and LH levels compared to the testosterone and LH levels just prior to the second injection. The mean acute-on-chronic (surge) changes in testosterone and LH levels will be analyzed based on subset of subjects have an 'acute-on-chronic' change at Visit 14 (Day 85), Visit 15 (Day 86), Visit 16 (Day 87) and Visit 17 (Day 98). The mean acute-on-chronic (surge) changes in testosterone and LH levels from just prior to the second injection through 14 days after the second injection of LMIS 25 mg (Day 98, week 14) will be summarized descriptively and a paired t-test or Wilcoxon signed-rank test will be used under significance level of 0.05. The summary results will be provided as Table 14.2.4~Table 14.2.5 for ITT population and Table 14.2.16~Table 14.2.17 for PP population.

- Effect of LMIS 25 mg on change of serum prostate-specific antigen (PSA) levels

- Effect of LMIS 25 mg on change of serum LH levels

The serum PSA levels and serum LH levels will be listed by subject in Listing 16.2.6.2 and Listing 16.2.6.3. The change from baseline for serum PSA levels at scheduled visit and serum LH levels at scheduled visit will be summarized descriptively and a paired t-test or Wilcoxon signed-rank test will be used with significance level of 0.05. The summary results will be provided as Table 14.2.6~Table 14.2.7 and Table 14.2.18~Table 14.2.19 for ITT and PP populations. Also, the PSA levels over time will be presented in Figure 14.2.5~Figure 14.2.6 for ITT and PP populations; the LH levels over time will be presented as Figure 14.2.3~Figure 14.2.4 for ITT and PP populations.

- The percentage of subject with PSA relapse defined as after achieving the serum PSA level ≤ 4 ng/mL post LMIS 25 mg injection but with an increase in serum PSA of >50% PSA nadir by Day 168 (week 24)

- The percentage of subject achieving normal serum PSA level (<4 ng/mL) on Day 168 ± 5 days (week 24)

The subject with PSA relapse is defined as after achieving the serum PSA level ≤ 4 ng/mL post LMIS 25 mg injection but with an increase in serum PSA of >50% PSA nadir by Day 168 (week 24), i.e. subject achieves the serum PSA level ≤ 4 ng/mL on Day 28 but with an increase in serum PSA of >50% PSA on Day 84 or Day 168, or subject achieves the serum PSA level ≤ 4 ng/mL on Day 84 but with an increase in serum PSA of >50% PSA on Day 168.

The incidence of PSA relapse will be presented as subject count, percentage, and exact 95% CI for binomial proportion in Table 14.2.8 and Table 14.2.20 for ITT and PP populations; and the percentage of subject achieves normal serum PSA level will be presented as Table 14.2.9 and Table 14.2.21 for ITT and PP populations. Besides, the additional analyses of PSA levels <4 ng/mL for subjects with elevated PSA at baseline as Table 14.2.11 and Table 14.2.23. It is noted that the normal serum PSA level shall be analyzed as <4 ng/mL rather than <4 ng/dL since it is typo on protocol.

- The percentage of subjects with enhanced serum testosterone concentration suppression to ≤ 20 ng/dL on Day 28 ± 1 day (week 4) and on Day 168 ± 5 days (week 24)

The percentage of subjects with a serum testosterone ≤ 20 ng/dL on Day 28 ± 1 day (week 4) and on Day 168 ± 5 days (week 24) will be analyzed using a standard large sample normal approximation to a Binomial distribution. The summary results included subject count, percentage and exact 95% CI for binomial proportion will be presented as Table 14.2.10 and Table 14.2.22 for ITT and PP populations.

Based on protocol, the testosterone level is assessed at Week 26 for the first enrolled 30 subjects. The additional analysis of subjects with a serum testosterone concentration suppressed to castrate levels (<= 50 ng/dL) at Week 26 will be presented as Table 14.2.12 and Table 14.2.24 for ITT and PP populations.

9.3 Sensitivity Analysis

The sensitivity analysis for primary efficacy endpoint will be performed by excluding all subjects from site CZ03 due to GCP compliance issues at this site. These subjects will be excluded from

both ITT and PP populations as another analysis scenario (ITT excluding subjects from site CZ03, and PP excluding subjects from site CZ03) for sensitivity analysis.

The summary results will be presented as Table 14.2.25~Table 14.2.26 and Table 14.2.27~Table 14.2.28 for ITT and PP populations.

10. EXTENT OF EXPOSURE AND DRUG COMPLIANCE

The study treatment LMIS 25 mg will be administered on Day 0 (Visit 2) and Day 84 (Visit 13; week 12). The study treatment date, time will be listed by subject in Listing 16.2.5.1. The proportion of subjects received first and second administration will be provided as Table 14.1.1.

11. SAFETY ANALYSIS

11.1 Adverse Events

All AEs will be coded by system organ class and preferred term for analysis. Treatment-emergent adverse event (TEAE) is defined as AEs occur after the first administration of study drug, or AEs occur before the first administration of study drug and worsen in severity after first dose. Unless otherwise specified, all adverse event summaries will include the TEAEs only. For purposes of the summary tables, AEs will be classified as either related or not related to study drug. The drug-related AEs are assessed as 'Definite', or 'Possible' related to study treatment. If the relationship is missing, the AE will also be assessed as drug-related AE. This summary will present the number and percentage of subjects, as well as number of events. For subject with the same AE but multiple different severity/relationship (which resolution date=onset date or resolution date=onset date+1, except they have different AE No), the multiple event will be combined as one AE with the maximum severity/ relationship category for analysis.

A general summary includes number of events, number and percentage of subjects reporting adverse events of all TEAEs will be provided in Table 14.3.1.1.1 according to the following categories:
• Subject with any TEAE
• Subject with any drug-related TEAE

Also, a general summary of all TEAEs will be provided in Table 14.3.1.1.2 according to the following categories:
• TEAEs by severity
• TEAEs by relationship
• Serious TEAEs

- Drug-related TEAEs by severity

Other summary tables for adverse events will be summarized by MedDRA system organ class and preferred term include:

Table 14.3.1.2: Treatment-Emergent Adverse Events - MedDRA

Table 14.3.1.3: Treatment-Emergent Adverse Events by Severity - MedDRA

Table 14.3.1.4: Treatment-Emergent Adverse Events by Relationship to Study Drug - MedDRA

Table 14.3.1.5: Treatment-Emergent Adverse Events for Grade ≥3 – MedDRA

Table 14.3.1.6: Drug-Related Treatment-Emergent Adverse Events by Severity – MedDRA

Table 14.3.1.9: Treatment-Emergent Adverse Events - MedDRA (Preferred Term over XX %)

The listing of all AEs will be provided in Listing 16.2.7.1. In addition, TEAEs leading to study discontinuation will be provided in Listing 16.2.7.2.

11.2 Serious Adverse Event

The summary of SAEs will be presented by MedDRA system organ class and preferred term, and this summary will present the number and percentage of subjects, as well as number of events:

Table 14.3.1.7: Treatment-Emergent Serious Adverse Events - MedDRA

Table 14.3.1.8: Treatment-Emergent Serious Adverse Events by Relationship to Study Drug - MedDRA

A listing of all serious adverse events will be provided in Listing 16.2.7.3.

11.3 Laboratory Evaluation

Clinical laboratory tests included hematology, biochemistry and urinalysis.

Hematology tests include complete blood count (CBC), Hb, Hct, RBC count, WBC count, WBC differential (neutrophils, eosinophils, basophils, lymphocytes, and monocytes), platelet count, and HbA1c.

Biochemistry tests include ALT, AST, ALP, total bilirubin, BUN, Serum Cr, electrolytes (K, Na, Mg, Ca and P), blood glucose, and lipid profile (LDL, HDL, triglycerides)

Urinalysis tests include pH, specific gravity, leukocyte, erythrocyte, urine glucose, nitrate, and protein..

By-subject-visit listings of measured values for clinical laboratory test data (hematology, biochemistry and urinalysis) will be prepared in Listing 16.2.8.1 ~ Listing 16.2.8.3. Observations outside the normal range will be flagged. The abnormal values will be flagged with 'L' (low) for

values below the lower limit of the laboratory's normal range, 'H' (high) for values above the upper limit of the laboratory's normal range or 'A' for values out of the laboratory's normal range. The abnormal values for clinical laboratory test data (hematology, biochemistry and urinalysis) will be prepared in Table 14.3.4. The record with observed value of clinical laboratory data below or above the detection limit will be imputed with the detection limit for analysis.

The baseline is defined as the last observation prior to first dose unless otherwise specified. The summary results of laboratory data (hematology, biochemistry and urinalysis) at baseline, EOS/ET Visit and change from baseline to the EOS/ET Visit will be summarized by descriptive statistics and paired t-test or Wilcoxon signed- rank test with significance level at 0.05. Results will be presented in Table 14.3.5.1~Table 14.3.5.3. The transition matrix of change in laboratory data (normal, abnormal NCS and abnormal CS status) between baseline and the EOS/ET Visit will be summarized as Table 14.3.5.4~Table 14.3.5.6.

11.4 Vital Signs and Physical Examination

Vital Signs

Individual subject vital signs (height, weight, body pressure, heart rate, respiration rate and body temperature) will be listed in Listing 16.4.1.

The baseline is defined as the last observation prior to first dose unless otherwise specified. The summary results of vital signs (body pressure, heart rate, respiration rate and body temperature) and weight at baseline, EOS/ET Visit, and the change from baseline will be summarized descriptively. Also the change from baseline to the EOS/ET Visit will be tested by paired t-test or Wilcoxon signed-rank test at a significance level of 0.05 in Table 14.3.6.

Physical Examination

Physical examination data (included: General appearance, Skin, Eyes, Ear/ Nose/ Throat (ENT), Head, Neck, Heart, Chest, Lungs, Abdomen, Extremities, Lymph nodes, Musculoskeletal and Neurological) will be listed in Listing 16.4.2, and will be summarized descriptively as count and percentage in Table 14.3.7.1. The transition matrix of physical examination (normal, abnormal NCS and abnormal CS status) will be summarized in Table 14.3.7.2.

11.5 Other Variables Related to Safety

Concomitant Medication and Non-Drug Therapy

Individual subject concomitant medication and non-drug therapy will be listed in Listing 16.2.5.2.

12-Lead ECG

Individual subject 12-Lead ECG data (heart rate, PR interval, RR interval, QRS duration, QT, QTc and overall interpretation) will be listed in Listing 16.4.3.

The baseline is defined as the last observation prior to first dose unless otherwise specified. The summary results of 12-lead resting ECG at baseline, EOS/ET Visit will be summarized descriptively in Table 14.3.8.1. The transition matrix for ECGs overall interpretation (normal, abnormal NCS and abnormal CS status) will be summarized in Table 14.3.8.2.

Additional 12-Lead ECG and PK Analyses for ECG Report

A separate ECG report will be provided with the results of the analyses in this section.

The following corrected QT interval for each visit and time point will be derived and considered the primary ECG assessment for the analysis in the ECG report.

QTcF: The QT interval in units of milliseconds (msec) corrected by the Fridericia formula will be calculated as follows:

$$QTcF = \frac{QT}{\sqrt[3]{(RR)}}$$, where RR interval will be expressed in units of seconds.

Descriptive statistics (number of subjects, mean, SD, 2-sided CI [90% for the QTcF interval or 95% for other parameters], median, 25th percentile, 75th percentile, minimum, and maximum) will be provided for baseline and each visit and time point post dose for results and change from baseline, denoted as ΔECG (i.e. ΔQTcF, ΔHR, ΔPR, ΔQRS), for the ECG population. Missing data will not be imputed. Unscheduled data will not be summarized or included in analyses. The means and 90% (in the case of ΔQTcF) or 95% CIs for the ΔHR, ΔPR, and ΔQRS values, will be displayed graphically by scheduled day and time point.

An analysis will be provided for the PK/ECG population based on a linear mixed effects model. The mixed-effects model will contain ΔQTcF as the dependent variable and include the corresponding leuprolide or testosterone serum concentrations in separate models with a random intercept and slope, day/time point as a categorical variable, and baseline QTcF (adjusted for the overall mean of subjects' baseline data included in the model) as the independent variables. The mixed effects model will be used to estimate, for all subjects in the PK/ECG analysis population, the predicted population mean ΔQTcF and its corresponding 2-sided 90% CI at mean C_{max} of the serum concentrations. Serum concentration values reported as below the limit of quantitation (BLQ) will be assigned a value of zero in this analysis. This analysis will be repeated for ΔHR, ΔPR, and ΔQRS, but 95% CIs will be presented rather than 90%.

The adequacy of the linear assumption between ΔECG interval and serum concentrations will be determined by adding a quadratic term to the mixed-effects model. If the quadratic term is different than zero, having a p-value <0.05, and an Akaike's information criteria (AIC) that is smaller in comparison to the linear model's AIC, then a quadratic term may be added. In addition, a transformation of the concentrations [e.g. log(Concentration/LLOQ), where LLOQ is the lower limit of quantitation of the assay and all values below the LLOQ are replaced with the LLOQ] may also be assessed. The best model fit will be determined by the lowest AIC, unless the model results are not clinically or physiologically sensible.

If convergence cannot be reached, adjustment to the model as follows will be considered: the random slope may be removed, an alternative covariance structure attempted, or as a last resort, the removal of the time effect may be considered.

The relevant SAS code statements are:
```
PROC MIXED DATA = DATA METHOD=REML;
    CLASS SUBJID ATPTN;
    MODEL CHG = CONC ATPTN BASEADJ /NOINT SOLUTION OUTP=PRED;
    RANDOM INTERCEPT CONC /TYPE=UN SUBJECT=SUBJID;
    ESTIMATE 'ΔECG at Cmax' CONC xx.x / CL ALPHA=0.1;
RUN;
```

In the above statements:
- CHG represents the ΔQTcF value (or corresponding secondary parameter);
- CONC represents measured serum concentrations of leuprolide or testosterone;
- ATPTN represents the day/time point;
- BASEADJ represents the numeric baseline minus the overall mean of all baseline values for the ECG parameter;
- TYPE=UN means that an unstructured covariance matrix will be used for the correlated random effects (INTERCEPT and CONC);
- xx.x in the ESTIMATE statement represents the estimated arithmetic mean C_{max} for leuprolide or testosterone.

Categorical Analyses for ECG Report

Categorical analyses of HR, PR, QRS, and QTcF will be performed to determine the number and percentage of subjects, who meet each of the following criteria at each day/time point and at the maximum/minimum QTcF (HR, PR or QRS) value postdose:
- Result QTcF $\leq$450, >450 and $\leq$480, >480 and $\leq$500, and >500 msec;

- Change from baseline ΔQTcF ≤ 30, >30 and ≤60, and >60 msec;
- PR Outliers (PR >200 msec and a 25% or greater increase from baseline);
- QRS Outliers (QRS >100 msec and a 25% or greater increase from baseline);
- HR Outliers (HR <50 beats/min and a 25% or greater decrease from baseline);
- HR Outliers (HR >100 beats/min and a 25% or greater increase from baseline).

Morphological ECG Diagnostic Statement Analyses for ECG Report

Abnormal morphological diagnostic statements will be tallied and tabulated for each day/time point and overall. The incidence rate of abnormal diagnostic statements will be tabulated for both baseline and post dose assessments, and also tabulated with abnormal diagnostic statements categorized as treatment emergent diagnostic statements (i.e., abnormal diagnostic statements not present on the baseline assessments). The variety of morphology statements with the same meaning will be aggregated into defined categories by the Cardiac Safety Expert and incorporated into the analysis dataset. For example, T-wave inversion in Lead V2 and T wave flattening in Lead II will both be categorized as nonspecific T-wave abnormality.

Adequacy of HR Correction for ECG Report

The adequacy of the correction formula for QTcF will be assessed by determining the linear relationship of QTcF interval to RR. Adequacy will be defined as a population QTcF:RR slope of < |0.045|, and a slope of < |0.045| in at least 50% of individual subjects. If QTcF interval is determined to be an inadequate correction, the QT interval with a study specific QTcSS will be calculated.

ECOG Performance Status

Individual subject ECOG performance status will be listed in Listing 16.4.4. The ECOG performance status will be summarized descriptively as Table 14.1.2.

Local Injection Site Reaction

Individual subject Local Injection Site Reaction will be listed in Listing 16.4.5. The local injection site reaction as recorded by Grade 0 (None), Grade 1 (Mild), Grade 2 (Moderate) and Grade 3 (Severe) will be summarized descriptively as count and percentage as Table 14.3.9.

Bone pain and urinary sign and symptoms (I-PSS)

Individual subject Bone pain and urinary sign and symptoms will be listed in Listing 16.4.6~ Listing 16.4.8. The summary results of VAS scale for bone pain measurement at baseline, EOS/ET Visit

and the change from baseline will be summarized descriptively in Table 14.3.10.1. Also, the change from baseline to EOS/ET visit will be tested by paired t-test or Wilcoxon signed-rank test at a significance level of 0.05. The urinary sign and symptoms at baseline and EOS/ET Visit will be summarized descriptively as Table 14.3.10.1. The transition status for urinary sign and symptoms by each scale* will be presented as Table 14.3.10.2. The quality of life will be presented as Table 14.3.10.3.

*For Urinary signs and symptoms Q1-Q6: 0 - None, 1 - Less than 1 time in 5, 2 - Less than half the time, 3 - About half the time, 4 - More than half the time, and 5 - Almost always.

For Urinary signs and symptoms Q7: 0 - None, 1 - 1 time, 2 - 2 times, 3 - 3 times, 4 - 4 times, 5 - 5 or more times.

For Urinary signs and symptoms quality of life: 0 - Delighted, 1 - Pleased, 2 - Mostly Satisfied, 3 - Mixed, 4 - Mostly Dissatisfied, 5 - Unhappy, 6 - Terrible

Unscheduled Assessments

The unscheduled assessment will be listed in Listing 16.4.9.

Telephone Contact

The telephone contact information will be listed in Listing 16.4.10.

12. COMPUTER METHODS

All statistical analyses will be conducted using SAS$^®$ software, Version 9.3 of the SAS System for Windows 7. Copyright$^©$ 2013 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.