

Protocol No.: FP01C-17-001

CLINICAL STUDY PROTOCOL

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)
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Phase: III
Sites: Multi-national, Multi-Center
Study Drug: Leuprolide Mesylate Injectable Suspension (LMIS 25 mg)
Version: 1.1
Date: 24 November 2017
Study Sponsor: Foresee Pharmaceuticals Co., Ltd.
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Compliance of Guidance and/or Rules and Regulations

This protocol is designed according to the International Conference on Harmonisation (ICH) guidance and the current national health authorities' rules and regulations. The study will be conducted in accordance with the design and specific provisions of this Department of Health (DOH) and institutional review boards (IRBs) approved protocol, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

INTERNAL SIGNATURE PAGE

I understand the obligations as an officer providing service in the organization(s) listed on this document, and agree to perform the study in compliance with the protocol, Good Clinical Practice (GCP) and the current rules and regulations set forth by the applicable health authorities and the International Conference on Harmonisation (ICH).

Affiliation	Name	Position	Signature	Date
Foresee Pharmaceuticals Co., Ltd		Sponsor		Nov 27, 2017
QPS Holdings		Project Manager		27/Nov/2017
QPS Holdings		Senior Director and Global Head, Pharmacokinetics		3 Dec 2017
QPS Holdings		Manager of Biostatistics & Data Management		24 Nov 2017
QPS Holdings		Medical Writer		24 Nov-2017

INVESTIGATOR'S SIGNATURE PAGE

I understand my obligations as a clinical trial investigator and agree to perform and report the study in compliance with the protocol, Good Clinical Practice (GCP) and the current rules and regulations set forth by the applicable health authorities, regulations and the International Conference on Harmonisation (ICH).

Name of Principal Investigator

Title

Signature

Date

_____	_____	_____	_____
_____	_____	_____	_____

PROTOCOL SYNOPSIS

I . Protocol title:

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

II . Objectives:

LMIS 25 mg is the mesylate salt of leuprolide and has the same biological activity profile as leuprolide acetate salt. It is a luteinizing hormone-releasing hormone (LH-RH) agonist acting as a potent inhibitor of gonadotropin secretion when given in therapeutic doses, and lowers testosterone levels to castrate levels. Leuprolide is the standard of care for palliative treatment of prostate cancer. This study is designed to evaluate the safety, efficacy, and pharmacokinetic (PK) profile of LMIS 25 mg when given as two separate subcutaneous injections administered 12 weeks apart in subjects with prostate cancer.

1. Primary objective:

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

2. Secondary objective:

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

III . Study drug:

1. Name: Leuprolide Mesylate Injectable Suspension (LMIS)
2. Dosage form: Leuprolide extended release injectable suspension (US) or Leuprolide prolonged-release suspension for injection (EU), prefilled and supplied in one sterile syringe, ready-to-use
3. Dose: 25 mg (as the mesylate salt)
4. Active ingredient: Leuprolide mesylate
5. Dosing schedule: 25 mg leuprolide mesylate administered subcutaneously, when given as two separate injections at 12 weeks apart (Day 0 and Day 84).
6. Mechanism of action:

The LH-RH agonist leuprolide, is known to inhibit pituitary gonadotropin secretion and suppress testicular and ovarian steroidogenesis. Continuous administration has been shown to maintain testosterone suppression. Serum testosterone concentrations in males have been reduced to levels associated with castration (≤ 50 ng/dL in serum). This effect is generally observed within two to four weeks after the start of treatment and is maintained as long as treatment continues. Induction and maintenance of castrate levels of serum testosterone in prostate cancer is a standard form of palliative treatment with a profound effect on cancer cell growth. LMIS 25 mg contains 25 mg leuprolide mesylate formulated in [REDACTED] and [REDACTED], to provide a sustained release of the bioactive leuprolide over a 3-month period after subcutaneous

administration.

7. Pharmacological category: Antineoplastic agent, gonadotropin releasing hormone analog

IV. Developmental phase: phase ☐ I ☐ II ☒ III ☐ IV ☐ Others

V. Study design:

1. ☐ Control: ☐ placebo

☐ active _____

☐ other _____

☒ Uncontrolled

2. Blinding: ☒ open-label ☐ evaluator blind ☐ single blind ☐ double blind

☐ double dummy ☐ other _____

3. Randomized: ☐ yes ☒ no

4. ☐ Parallel ☐ Cross-over ☒ Other Single-arm, open label

5. Duration of study: approx. 24 weeks

6. Titration: ☐ forced ☐ optional ☒ none

7. ☒ Multi-national ☒ Multi-center ☐ Single center

VI. Endpoints

1. Primary endpoint:

- To determine the percentage of subjects with a serum testosterone concentration suppressed to castrate levels (≤ 50 ng/dL) on Day 28 ± 1 day (week 4) following administration of LMIS 25 mg, and the proportion of subjects with serum testosterone suppression (≤ 50 ng/dL) maintained from Day 28 ± 1 day (week 4) through Day 168 ± 5 days (week 24)

2. Secondary Endpoints:

2.1 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 (Day 98, week 14)
- Effect of LMIS 25 mg on serum LH levels
- Effect of LMIS 25 mg on serum prostate-specific antigen (PSA) levels
- 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 ± 5 days (week 24)
- The percentage of subject achieving normal serum PSA level (<4 ng/dL) on Day 168 ± 5 days (week 24)
- The percentage of subjects with enhanced serum testosterone concentration suppression

to ≤ 20 ng/dL on Day 28 ± 1 day (week4) and on Day 168 ± 5 days (week 24)

2.2 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 assessed 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, S_{Cr}), 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

2.3 Pharmacokinetic:

- The serum pharmacokinetic profile of leuprolide for up to 26 weeks following 2 subcutaneous injections of LMIS 25 mg given 12 weeks apart will be determined from baseline to Day 182 (week 26) in a subset of subjects. This subset of subjects will be followed for an additional two weeks to week 26 (Day 182) after the second injection. The PK parameters of leuprolide will be determined during the study period, including C_{max} , T_{max} , C_{week4} , C_{week12} , $AUC_{0-week4}$, $AUC_{0-week12}$, $C_{avg(0-week12)}$ after each dose.

2.4 Exploratory:

- The PK/PD analysis (serum testosterone and leuprolide levels) in the first enrolled 30 subjects on Day 182 (week 26)

VII. Selection criteria:**1. Main inclusion criteria:**

- (1) Males aged ≥ 18 years old
- (2) Males with histologically confirmed carcinoma 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 ≤ 2
- (6) Life expectancy of at least 18 months
- (7) Laboratory values
 - Absolute neutrophil count $\geq 1,500$ cells/ μ L
 - Platelets $\geq 100,000$ cells/ μ L
 - Hemoglobin ≥ 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 ≤ 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 $\leq 9.5\%$
 - 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: <0.1 g/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

2. Main exclusion criteria:

- (1) Receipt of chemotherapy, immunotherapy, cryotherapy, radiotherapy, or anti-androgen therapy concomitantly, or within 8 weeks prior to screening visit, for treatment of carcinoma 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

3. Withdrawal criteria:

- (1) Lost to follow-up
- (2) Subject withdrew consent

- (3) In investigator's opinion that treatment with prohibited medications is needed
- (4) Adverse event/serious adverse event
- (5) Protocol violation (please provide specific reason)
- (6) Lack of efficacy as determined by investigator
- (7) Subjects with persistent, non-castrate serum testosterone levels (>50 ng/dL)
- (8) Other

VIII. Study design:

This is a multi-national, multi-center, open-label, single-arm study to determine the efficacy, safety, and pharmacokinetic profile of LMIS 25 mg in subjects with prostate cancer. The study duration is approximately 24 weeks. Two doses of LMIS 25 mg will be given to subjects by separate subcutaneous injection approximately 12 weeks apart in an unblinded manner. LMIS 25 mg will be administered on Day 0 (Visit 2) and Day 84 (Visit 13; week 12). At the end of week 12 (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, and PK/PD parameters for another 12 weeks (Day 168; week 24).

Blood samples will be collected at baseline (Day 0) before LMIS 25 mg administration, immediately after LMIS 25 mg injection, and at specified time points to determine the pharmacokinetic (PK) and pharmacodynamics profiles of leuprolide and serum testosterone levels, respectively. The serum levels of testosterone, leuprolide, PSA, and luteinizing hormone (LH) will be measured during the study period. The PK parameters of leuprolide will be determined during the study period.

The study period in the first enrolled 30 subjects (considered as a subset of subjects) will be extended for another 2 weeks post Day 168 (Day 182 ± 3 days; week 26; Visit 23) to obtain the extended PK/PD profile of serum leuprolide and testosterone levels. Approximately 133 subjects will be enrolled in this study.

All AEs and serious adverse events (SAEs) which occur during the study period will be recorded in the case report forms (CRFs) and followed until resolution or until they are considered stable. In addition, SAEs will be recorded and reported as required by both local and international regulatory requirements.

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

IX. Concomitant treatment:**1. Permitted:**

- (1) Bisphosphonates will be permitted during the study.
- (2) Denosumab will be permitted during the study.
- (3) Supplementation of vitamin D and calcium will be allowed during the study if, in the investigator's opinion, it is needed for the subject's health.
- (4) Plain, over-the-counter multi-vitamins will be permitted during the study.
- (5) Glucocorticosteroids will be allowed if being used as a replacement therapy.
- (6) Pain medication will be allowed if it is an over-the-counter or prescription medication as prescribed by a physician and meets the criteria outlined in Appendix IV.
- (7) Oral hypoglycemics will be allowed for control of Type II diabetes.
- (8) Radiation for pain control will be allowed during the study.

2. Prohibited:

The medications below are prohibited during the treatment period:

- (1) Other gonadotropin-releasing hormones
- (2) Other chemotherapy, immunotherapy, cryotherapy, radiotherapy for treatment of prostate carcinoma
- (3) Any OTC medication other than those listed in the Concomitant Treatment section
- (4) Dietary supplements, herbal supplements, or herbal tea
- (5) Insulin
- (6) Anti-androgens
- (7) 5-alpha reductase inhibitors
- (8) Systemic corticosteroids > 10 mg/d

X. Statistics:

- 1. Primary hypothesis:** ☐ superiority ☐ non-inferiority
☐ equivalence ☒ other

- 2. Sample size :** Approximately 133 subjects will be enrolled. It is anticipated that > 100 subjects will receive 2 separate doses of LMIS 25 mg given at 12 weeks apart. A 10% drop out rate is estimated.

- 3. Efficacy population:** ☒ ITT ☒ PP ☐ other:

- (1) The Intention-To-Treat (ITT) population will consist of any subject receiving at least one dose of LMIS 25 mg.
- (2) 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.

4. Safety population: ☐ ITT ☐ PP ☒ other:

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

5. Statistical method(s) for efficacy/ safety evaluations:

- (1) The ITT and PP populations will be used in the efficacy analyses. Any subject receiving a dose of LMIS 25 mg will be included in the safety analysis.
- (2) For descriptive statistics, continuous variables will be presented as number of observations, mean, standard deviation (SD), median, range, Hodges-Lehmann estimator and 95% CI. Categorical variables will be presented by frequency and percentage. Changes from baseline will be tested by a paired t-test or Wilcoxon signed-rank test for continuous variables using a significance level of 0.05.
- (3) For primary endpoints, the percentage of subjects with a serum testosterone of ≤ 50 ng/dL (castrate level) on Day 28 ± 1 day (week 4) and on Day 168 ± 5 days (week 24) will be analyzed using a standard large sample approximation to a Binomial distribution. The percentage of subjects with a serum testosterone of ≤ 50 ng/dL (castrate level) from Day 28 ± 1 day (week 4) through Day 168 ± 5 days (week 24) will be analyzed using the Kaplan-Meier approach.
- (4) The following efficacy analyses will be provided in detail in the statistical analysis plan:
 - The proportion of subjects with testosterone suppression (≤ 50 ng/dL) from Day 28 (week 4) through Day 168 ± 5 days (week 24)
 - Subjects exhibiting post-suppression breakthrough of serum testosterone to >50 ng/dL
 - Time to event: A subject with a testosterone level > 50 ng/dL between Days 28 and 168 is considered to have an event.
- (5) The mean acute-on-chronic (surge) changes in serum testosterone level and LH level will be summarized by descriptive statistics; the change from the baseline levels of testosterone and LH post the second injection of LMIS 25 mg will be summarized descriptively.
- (6) The serum PSA levels and serum LH levels during the study will be summarized by descriptive statistics, and the change from baseline will also be summarized descriptively and a paired t-test or Wilcoxon signed-rank test will be used, data significance level of 0.05.
- (7) The PSA relapse is defined as any subjects who achieve the serum PSA level ≤ 4 ng/mL post LMIS 25 mg injection but then have an increase in serum PSA of $>50\%$ PSA nadir by Day 168 (week 24). This endpoint will be presented as a count, percentage and 95% CI.
- (8) The percentage of subjects with an enhanced serum testosterone ≤ 20 ng/dL by Day 28 ± 1 day (week 4) and Day 168 ± 5 days (week 24) will be analyzed using a standard large sample normal approximation to a Binomial distribution.

- (9) For safety assessment, the local injection site reaction will be summarized descriptively.
- (10) The summary results at baseline (Day 0) and the change of continuous variables including bone pain measurement (by VAS scale), urinary signs and symptoms (by the I-PSS sheet), vital signs and lab data will be summarized descriptively, and a paired t-test or Wilcoxon signed-rank test will be used at a significance level of 0.05. The transition matrix for categorical variables will be presented.
- (11) AEs will be coded with MedDRA, and a summary frequency table of AEs will be provided. The severity and relationship to study medication of AEs will be summarized as well. Furthermore, if any SAE occurs, a summary of SAEs will be presented and listed in tables.
- (12) For PK profile analysis, arithmetic means, standard deviations (SDs) and coefficients of variation (CV) will be calculated.
- (13) All statistical tests will be two-sided and evaluated at the 0.05 level of significance.
6. Planned interim analysis: ☐yes ☒no

Table 1a. Study Schedule: VISITS 1-13

	Scrn	1 st Dose				Follow Up										2 nd 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		X ⁵								X				X		X ⁵	
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 hormone ⁷	X	X				X	X#	X	X#	X	X	X	X#	X	X	X			

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	Scrn	1 st Dose				Follow Up										2 nd 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
Lab chemistry																			
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 (I-PSS)

* 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 Day 140 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 visit, Day 84, and Day 168 (EOS/ET).

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

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that, additional samples for testosterone may be ordered by the investigator at their discretion and done 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 BA lab using a validated ELISA 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 BA 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, week 4), a \pm 1-day window is allowed. At Visits 10 and 12 (Day 42 to Day 77; week 6 to week 11), a \pm 3-day window is allowed. At Visits 13 to 16 (Day 84 for the second dose injection, week 12 to Day 87), only \pm 1-day window is allowed. At Visits 17 to 21 (Day 98 to Day 161), a \pm 3-day window is allowed. At Visit 22 (Day 168), a \pm 5-day window is allowed. At Visit 23 (Day 182), a \pm 3-day window is allowed.

Table 1b Study Schedule: VISITS 14-EOS/ET (Visit 22 or 23)

	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 sign 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:

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Respiratory rate; Scrn: Screening; BP: Blood pressure; VAS: Visual Analogue Scale; I-PSS: International Prostate Symptom Score (I-PSS)

* 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 Day 140 Visit (Visit 20, week 20), adjust the scheduled date according to the date when the first injection was received

+ 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.

Procedures/ examinations for the first enrolled 30 subjects only.

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, and Day 168 (EOS/ET).

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 BA lab using a validated ELISA 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 BA 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 \pm 1-day window is allowed. At Visits 10 and 12 (Day 42 to Day 77), a \pm 3-day window is allowed. At Visits 13 to 16 (Day 8 for the second dose injection, week 12, to Day 87), only \pm 1-day window is allowed. At Visits 17 to 21 (Day 98 to Day 161), a \pm 3-day window is allowed. At Visit 22 (Day 168), a \pm 5-day window is allowed. At Visit 23 (Day 182), a \pm 3-day window is allowed.

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LIST OF ABBREVIATIONS AND TERMS

TERM	DEFINITION
ADL	Activities of Daily Living
ADR	Adverse Drug Reactions
ADT	Androgen Deprivation Therapy
AE(s)	Adverse Event(s)
ALT (SGPT)	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ANC	Absolute Neutrophil Count
Approx.	Approximately
AST (SGOT)	Aspartate Transaminase
BDM	Biostatistics & Data Management
BLQ	Below Limit of Quantitation
BP	Blood Pressure
BT	Body Temperature
BUN	Blood Urea Nitrogen
Ca	Calcium
CBC	Complete Blood Count
CI	Confidence Interval
CRC	Clinical Research Coordinator
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
EC	Ethics Committee
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
ENT	Ear, Nose, and Throat
ET	Early Termination
EOS	End of Study
FDA	Food and Drug Administration

TERM	DEFINITION
F/U	Follow-up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GnRH	Gonadotropin-Releasing Hormone
Hb	Hemoglobin
Hct	Hematocrit
HDL	High Density Lipoprotein
hpf	High power field
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IP	Investigational Product
I-PSS	International Prostate Symptom Score
IRB	Institutional Review Board
IS	Internal Standard
ITT	Intent-to Treat
IV	Intravenously
K	Potassium
LC/MS/MS	Liquid Chromatography-tandem Mass Spectrometry
LDL	Low Density Lipoprotein
LH	Luteinizing Hormone
LH-RH	Luteinizing Hormone-Releasing Hormone
LMIS	Leuprolide Mesylate Injectable Suspension
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Magnesium
Na	Sodium
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NMP	N-methyl-2-pyrrolidone
OTC	Over-the-Counter
P	Potassium
PD	Pharmacodynamics
PI	Principal Investigator

TERM	DEFINITION
PK	Pharmacokinetics
PLA	Poly (D, L-lactide)
PLGA	Poly (D, L-lactide-co-glycolide)
PP	Per-Protocol
PR	Partial Response
PS	Performance Status
PSA	Prostate Specific Antigen
QC	Quality Control
RBC	Red Blood Cell
RR	Respiratory Rate
SAE(s)	Serious Adverse Event(s)
SBP	Systolic Blood Pressure
S _{Cr}	Serum Creatinine
Scrn	Screening
SOC	System Organ Class
SOP	Standard Operation Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Total Bilirubin
TEAE	Treat emergent adverse event
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WBC	White Blood Cell
WHO	World Health Organization

1. INTRODUCTION

1.1. Background Information

Prostate cancer is one of the leading causes of deaths in men globally^[1, 2]. In the absence of screening, disease progression of prostate cancer is asymptomatic in early stages and therefore, it is often diagnosed late. More than 90% of prostate tumors are found locally or regionally. Men aged 65 years or older are the major group at risk; other common risk factors include ethnicity, family history, dietary habits, smoking, and occupational exposure. Since 1990, the use of molecular screening methods has greatly increased the diagnosis rate and the percentages of patients receiving early treatments^[3].

Therapeutic choice for the treatment of prostate cancer is determined based on age, tumor grade and stage as well as other medical conditions. In conjunction with radiation and chemotherapy, hormonal therapy is widely used in the treatment of prostate cancer patients. Recent evidence has suggested that disease progression of prostate cancer is highly dependent on androgen levels. Long term hormonal control helps to alleviate the growth of proliferating prostate cancer cells and may be beneficial to patient survival^[4, 5]. On this basis, the development of androgen deprivation therapy (ADT) has been the mainstay of hormonal treatment for prostate cancer over the years. Thus, various types of pharmaceutical agents have been developed to produce the effect of medical castration. These agents include gonadotropin-releasing hormone (GnRH) agonist, GnRH antagonist, estrogen agonist, and androgen inhibitors^[6, 7, 8].

1.2. The Development of Leuprolide Acetate

Chronic administration of GnRH agonist leads to down-regulation of GnRH receptors in the pituitary gland, which results in the complete suppression of luteinizing hormone (LH), follicle-stimulating hormone, and gonadal steroids after an initial stimulatory phase. Among currently available GnRH agonists, administration of leuprolide acetate has shown satisfactory efficacy with tolerable side-effects^[9].

Leuprolide acetate is the synthetic analogue of naturally-occurring GnRH. Chemically modified on residues 6 and 10, leuprolide acetate possesses higher binding affinity to androgen receptors and is more stable than the naturally-occurring GnRH^[10]. Within weeks of treatment, prostate cancer patients receiving leuprolide acetate showed significant suppression of serum testosterone level, similar to surgical castration. Treatment with a GnRH agonist is considered the standard of care for palliative therapy for prostate cancer patients.

1.3. Study Rationale

Leuprolide acetate (Lupron Depot[®]) was initially given by daily subcutaneous injections when it was first approved in 1985. Eligard[®] 22.5 mg (Sanofi-Aventis US, LLC) was a novel formulation incorporating leuprolide acetate with a biodegradable polymer matrix (Atrigel[®] delivery system). It was designed to deliver 22.5 mg of leuprolide acetate at a controlled rate over a 3-month period of time. Thorough mixing of leuprolide acetate lyophilized powder and the co-polymer, poly (D,

L-lactide-co-glycolide) (PLGA) prior to subcutaneous injection was essential and critical for delivering a sufficient dose. Improvements in depot formulations enabled convenient subcutaneous or intramuscular injection of leuprolide given in the monthly basis. A variety of sustained-release formulations are now commercially available and some in development, including leuprolide mesylate. The current investigational product, LMIS 25 mg (Foresee Pharmaceuticals Co., Ltd), is the mesylate salt of leuprolide with biological activity comparable to Eligard[®] 22.5 mg. LMIS 25 mg is designed to deliver 25 mg of leuprolide mesylate at a controlled rate over a 3-month period. The LMIS 25 mg formulation uses the same solvent, [REDACTED]. However, a different polymer system, [REDACTED] is applied to allow sustained release of leuprolide. LMIS 25 mg successfully solved the stability issues of Eligard[®]. Thus, LMIS 25 mg is supplied as a single, sterile, pre-filled syringe. It is ready-to-use; no premixing is required prior to subcutaneous injection.

Preclinical investigations with LMIS 25 mg have shown similar biological activity, pharmacokinetic, pharmacodynamic, and safety profiles, when compared to Eligard[®] 22.5 mg. A 3-month depot leuprolide acetate formulation has been shown to possess similar clinical efficacy and side effect profiles to marketed depot formulations. The 3-month depot formulation is considered a convenient treatment option for patients with prostate cancer [11, 12, 13, 14, 15, 16, 17, 18]. A 12-month, open-label, multicenter clinical trial showed that in patients with prostate cancer, 6-month leuprolide acetate injections induced reliable and effective suppression of testosterone comparable to bilateral orchiectomy [17]. A recent large-scale study also has shown favorable results [9] with 6-month leuprolide acetate treatment. Notably, a lower dose of leuprolide acetate also showed efficacy in achieving castrate testosterone levels and with tolerable safety profile in Asian prostate cancer patients [19]. Thus, different dosage forms of leuprolide acetate have been developed.

With regard to human use experience with leuprolide mesylate injectable suspension (LMIS) developed by Foresee, a recent Phase III study using LMIS 50 mg as a 6-month depot formulation in prostate cancer patients (study number FP01C-13-001) was conducted. The study design of FP01C-13-001 was in accordance with prior discussion with the FDA and was conducted in the USA, Europe, and Taiwan. Briefly, 137 subjects with prostate cancer were enrolled in the multi-national, multi-center, single-arm, open-label study. These subjects were treated with 2 subcutaneous doses of LMIS 50 mg given 6 months apart. Primary endpoints included safety and tolerability assessments throughout 1 year of treatment; efficacy evaluation was based on the percentage of subjects with a serum testosterone concentration suppressed to castrate levels (≤ 50 ng/dL) by Day 28 \pm 1 day following the first injection of LMIS 50 mg and the percentage of subjects with serum testosterone suppression (≤ 50 ng/dL) from Day 28 through Day 336 (remaining duration of the study). The assessment of PK profile of leuprolide mesylate was also included.

In the Phase III study (study number FP01C-13-001), a total of 137 subjects were enrolled and received at least one dose of the study drug (ITT population), and 124 subjects completed the study without major protocol violations that would affect the primary efficacy endpoint (per-protocol population (PP)). The primary efficacy endpoint was achieved in 97.0% of subjects in both ITT and PP populations. The 95% confidence interval from Kaplan-Meier estimates was (92.2%, 98.9%), and the 95% Repeated-Confidence Interval (RCI) was (92.5%, 99.4%). By Day 28, mean testosterone concentration was suppressed below the castrate level to 17.6 ng/dL, and the

suppression rate was 98.5% (135 out of 137 subjects achieved medical castration). No mean increase in testosterone was observed after the second injection. Four subjects did not have successful suppression of testosterone by the primary efficacy endpoint analysis, two of whom failed to achieve castration level on Day 28 and the other two had transient testosterone escapes.

The secondary endpoints of this study were to determine the effect of LMIS 50 mg on (1) the proportion of subjects exhibiting post-suppression excursions of serum testosterone to > 50 ng/dL, either through “breakthrough” (i.e., episodes unrelated to LMIS 50 mg dosing), or through the “acute-on-chronic” surge (i.e., related to the second dose of LMIS 50 mg), (2) the effect of LMIS 50 mg on serum PSA levels, (3) the effect of LMIS 50 mg on serum LH levels.

In the FP01C-13-001 study, only two subjects exhibited post-suppression excursions. These post-suppression excursions occurred after the second dose of LMIS 50 mg injection on Day 168 to Day 171. These effects were attributed to mild, transient acute-on-chronic surge. Serum testosterone levels in all the above subjects returned to below the castrate level shortly thereafter. No other breakthrough of serum testosterone to > 50 ng/dL was observed in this study.

The administration of LMIS 50 mg significantly reduced the serum PSA levels from the first injection until the end of study in both ITT and PP populations. The mean serum PSA level was reduced by almost 85% and 89%, in ITT and PP populations, respectively, compared to the mean baseline level. The administration of LMIS 50 mg also significantly reduced the mean serum LH levels after the first injection and this effect remained until the end of study. The average serum LH level was significantly reduced by 98% by Day 336 in both ITT and PP populations.

With regard to the safety of LMIS 50 mg in prostate cancer patients, of 137 subjects enrolled, the most common ($\geq 5\%$) TEAEs observed by preferred term was hot flush (48.9%), followed by hypertension (14.6%), pain in extremity (9.5%), injection site pain (7.3%), arthralgia (6.6%), fatigue (6.6%), nocturia (5.8%), back pain (5.1%) and nasopharyngitis (5.1%). With regard to the severity of TEAEs, most TEAEs were mild or moderate. Of 137 enrolled subjects, 62% subjects (85/137) were reported with drug-related AEs determined by investigators. The most common ($\geq 5\%$) drug-related AEs observed by preferred term was hot flush (48.2%), followed by injection site pain (7.3%) and fatigue (5.8%).

There were 3 deaths reported (3/137, 2.2%) in this study. All three fatal events were determined to be unrelated to the use of LMIS 50 mg by investigator. Overall, the administration of LMIS 50 mg demonstrated a tolerable safety profile similar to that of Eligard[®] 45 mg. A 1-year (2 years total exposure) safety extension study of LMIS 50 mg in prostate cancer patients has been initiated and is currently ongoing to follow up on the safety profile of LMIS 50 mg (FP01C-13-001-EX).

Foresee Pharmaceuticals is currently developing leuprolide mesylate 25 mg injectable suspension (LMIS 25 mg) as a line-extension product. Foresee expects that the subcutaneous injection of LMIS 25 mg will be equivalent or similar to the pharmacodynamic effects of the Eligard[®] 22.5 mg 3-month depot formulation in subjects with prostate cancer. The current study is designed to determine the safety, tolerability, and efficacy of LMIS 25 mg for up to 24 weeks of exposure in subjects with prostate cancer. Moreover, the pharmacokinetic profile of serum leuprolide following 2 separate subcutaneous injections of LMIS 25 mg will be evaluated.

2. STUDY OBJECTIVE AND ENDPOINTS

LMIS 25 mg is supplied as a pre-mixed drug product containing 25 mg leuprolide mesylate (21 mg of leuprolide free base) formulated in [REDACTED] to control and sustain the release of the bioactive leuprolide over a 3-month period following subcutaneous administration. The purpose of this study is to evaluate the safety, efficacy, and pharmacokinetic behavior of LMIS 25 mg in subjects with prostate cancer after two subcutaneous depot injections given 12 weeks apart (on Day 0 and Day 84).

2.1. Study Objective

2.1.1. Primary objective

- 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

2.1.2. Secondary objective

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

2.2. Study Endpoints

2.2.1. Primary endpoints

The primary endpoints of efficacy are to determine:

- The percentage of subjects with a serum testosterone concentration suppressed to castrate levels (≤ 50 ng/dL) on Day 28 ± 1 day (week 4) following the first injection of LMIS 25 mg, and the proportion of subjects with serum testosterone suppression (≤ 50 ng/dL) from Day 28 ± 1 day (week 4) through Day 168 ± 5 days (week 24) until the end of the study

2.2.2. Secondary endpoints

2.2.2.1 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 ≤ 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/dL) on Day 168 ± 5 days (week 24)
- 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)

2.2.2.2 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, S_{Cr}), 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

2.2.2.3 Pharmacokinetic

- The serum pharmacokinetic profile of leuprolide for up to 26 weeks following 2 subcutaneous injections of LMIS 25 mg given 12 weeks apart will be determined from baseline to Day 168 (week 24) in a subset of subjects. This subset of subjects will be followed for an additional two weeks to week 26 (Day 182) after the second injection.

The PK parameters of leuprolide will be determined during the study period, including C_{max} , T_{max} , C_{week4} , C_{week12} , $AUC_{0-week4}$, $AUC_{0-week12}$, $C_{avg(0-week12)}$ after each dose.

2.2.2.4 Exploratory:

- The PK/PD analysis (serum testosterone and leuprolide levels) in the first enrolled 30 subjects on Day 182 (week 26)

The extended serum pharmacokinetic/pharmacodynamics profile of leuprolide and testosterone levels will be followed for additional 2 weeks post Day 168 in the first enrolled 30 subjects (PK subset).

3. STUDY DESIGN

3.1. Overall 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 (≤ 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.

Pharmacokinetic assessments of serum leuprolide levels will be performed using a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) method. To evaluate the sustained castration testosterone level after two doses of LMIS 25 mg injections, the first 30 subjects will have extended sampling time points to establish the full PK/PD profile of serum leuprolide by collecting blood samples on Day 0 (prior to the first dose of LMIS 25 mg, and at 2, 4, and 8 hours post-dose), Days 1, 2, 3, 7, 14, 21, 28, 42, 56, 77, 84 (week12: prior to the second dose and at 2, 4,

and 8 hours post the second dose), Days 85, 86, 87, 98, 112, 126, 140, 161, 168 (week 24) and 182 (week 26, end of study (EOS)).

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 (week 12: 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)).

The pharmacokinetic parameters of leuprolide will be determined during the study period using non-compartmental approaches with Phoenix WinNonlin[®], including C_{max} , T_{max} , C_{week4} , C_{week12} , $AUC_{0-week4}$, $AUC_{0-week12}$, $C_{avg(0-12week)}$ after each dose. The Day 182 (week 26) leuprolide serum concentration data from the first 30 subjects will also be determined.

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 (EMA/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 validated, commercial assay kits at the BA lab.

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.

4. ELECTION AND WITHDRAWAL OF SUBJECTS

The criteria for enrollment must be adhered explicitly.

4.1. Inclusion Criteria

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

1. Males aged ≥ 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 ≤ 2
6. Life expectancy of at least 18 months
7. Laboratory values
 - Absolute neutrophil count $\geq 1,500$ cells/ μ L
 - Platelets $\geq 100,000$ cells/ μ L
 - Hemoglobin ≥ 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 ≤ 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 $\leq 9.5\%$
 - 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: <0.1 g/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

4.2. 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

4.3. Withdrawal Criteria

Discontinuation from study is defined as discontinuation of all study visits and examinations. Participants may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, or fail to return for visits, or become lost to follow up for any other reason.

Subjects will be withdrawn from the study if any of the following occurs during the study period, i.e. from screening visit to the end of study (EOS):

- (1) Lost to follow-up
- (2) Subject withdrew consent
- (3) In investigator's opinion that treatment with prohibited medications is needed
- (4) Adverse event/serious adverse event
- (5) Protocol violation (please provide specific reason)
- (6) Lack of efficacy as determined by investigator
- (7) Subjects with persistent, non-castrate serum testosterone levels (>50 ng/dL)
- (8) Other

Subjects who are withdrawn due to AEs or SAEs will be followed until these events are resolved or until the event is considered stable.

Should a subject's testosterone concentration be above the castration level (> 50 ng/mL) at or after Visit 9 (Day 28/week 4), an extra visit for confirmation of testosterone level will be issued immediately. Subjects will be withdrawn from the study at the time of confirmation from the repeat testosterone analysis. The investigators can provide other alternative treatments promptly to these withdrawn subjects in accordance with standard clinical practice.

5. STUDY TREATMENT

5.1. Treatment Plan Summary

This is a multi-national, multi-center, Phase III, open-label, single dose study. All eligible subjects will receive two separate doses of LMIS 25 mg by subcutaneous injection with 12 weeks apart.

LMIS 25 mg is a pre-mixed drug product containing 25 mg leuprolide mesylate (equivalent to 21 mg of leuprolide free base) formulated in a suspension of NMP and PLGA to control and sustain the release of the bioactive leuprolide over a 3-month period after a single subcutaneous administration. It is intended to be used as the palliative treatment of prostatic cancer.

Subjects with prostate cancer will be screened and enrolled into this study if eligible. After enrollment, subjects will receive the first dose of LMIS 25 mg by subcutaneous injection on Day 0 and then receive the second dose of LMIS 25 mg on Day 84 (week 12 after the first dose). All subjects will be followed for at least another 12 weeks after the second dose administration.

5.2. Treatment Assignment

Subjects will be assigned a screening number after the subject signs the informed consent document. Only qualified subjects will be enrolled and uniquely identified by an enrolled number. The enrolled number should be recorded on the CRF.

5.3. Description of Study Drug

Leuprolide is a synthetic nonapeptide analog and agonist of the naturally occurring LH-RH or GnRH receptor. Leuprolide is a more potent agonist of the GnRH receptors relative to the natural GnRH peptide due to its increased affinity for the GnRH receptors and longer half-life. As a GnRH agonist, leuprolide functions as an inhibitor of gonadotropin secretion when administered continuously in therapeutic doses. Leuprolide acetate was introduced in 1985 for the treatment of prostate cancer as an alternative to surgical castration and estrogen therapy (NDA 19-010). Subjects with prostate cancer tend to accept this palliative treatment from a psychologic standpoint because it avoids surgical castration and also because its effects on gonadotropin are reversible when treatment is discontinued.

Foresee Pharmaceuticals is developing LMIS 25 mg for the palliative treatment of prostate cancer. LMIS 25 mg is prefilled and supplied in a ready-to-use sterile syringe for subcutaneous injection and it is expected to deliver 25 mg leuprolide mesylate per syringe in a biodegradable poly (D,L-Lactide-co-Glycolide) (PLGA) polymer formulation dissolved in a biocompatible solvent, N-methyl-2-pyrrolidone (NMP). Investigational product dose administration procedures are outlined in the Investigational Product Instruction Manual.

5.4. Rationale for Dose

The LMIS 25 mg dosage form has been developed to deliver bioactive leuprolide over a 3-month period after subcutaneous administration with a controlled-release profile similar to that of the

Eligard® 22.5 mg formulation. The LMIS 25 mg dosage and its use as a sustained-release or depot dosage form have shown to be both efficacious and safe in similar leuprolide products (i.e., Eligard® 22.5 mg) as summarized in the Investigator Brochure.

5.5. Warning and Precautions

LMIS 25 mg contains the active pharmaceutical ingredient of leuprolide. Thus, the use of LMIS 25 mg may cause adverse events similar to the established AE profiles observed in the use of leuprolide acetate.

Leuprolide acetate has the following established significant AEs:

- Transient clinical testosterone flare reaction in men with prostate cancer
- Osteoporosis

Like other LH-RH analogs, leuprolide acetate causes a transient increase in the serum concentration of testosterone during the first week of treatment. This effect may cause subjects to experience a worsening of symptoms or an onset of new symptoms including bone pain, neuropathy, hematuria, or ureteral or bladder outlet obstruction. Long-term use of an LH-RH agonist has been reported to decrease bone mineral density which can increase the risk of osteoporosis and skeletal bone fractures.

Other reported adverse events of leuprolide acetate include hypogonadism, reduction in glucose tolerance, metabolic syndrome, anemia, and prolongation of the QT/QTc interval.

5.6. Packaging and Labeling

LMIS 25 mg will be provided to the investigator in a single use kit by Foresee Pharmaceuticals Co., Ltd, or its designee. A sterile syringe pre-filled with LMIS 25 mg suspension will be supplied with a standard, sterile 18 gauge needle, a plunger rod, and a backstop to facilitate subcutaneous injection. LMIS 25 mg pre-filled syringes are individually packaged in blisters which are placed in individual carton boxes. LMIS 25 mg kits are to be stored at 2 – 8°C.

Each site will be provided with emergency back-up kits of study drug in case of contamination or other loss. The investigational sites will be directed to assign specific emergency kits to individual subjects when needed by matching the subject's code to the kit label.

All investigational products are labeled with the information below; however, any additional information appearing on the label will conform to local regulatory requirements.

- Product name
- Batch number
- Protocol number
- Kit number
- Storage instructions
- Sponsor address
- Use-by date
- “Clinical trial use only”

The details noted on the labels are in accordance with applicable regulatory requirements.

5.7. Supply, Delivery, Storage of Study Drug

LMIS 25 mg (investigational product, IP) is supplied by Foresee Pharmaceuticals Co., Ltd. The IP will be shipped to the study site by a contracted delivery agent. The representative PI of the site will be in charge of the management and dispensation of the IP. Shipping receipts from receipt of IP or shipment of IP should be retained by the investigational site as part of the study records.

LMIS 25 mg kits will be managed and stored at 2 – 8°C, safely, and properly in a secured, lockable area by a designated, qualified person at the investigative site.

5.8. Drug Dispensation and Accountability

The investigational product will be administered to the subject by site staff designated by PI. The investigators and/or pharmacists must maintain records of the IP's delivery to the study site, the IP inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused IP. These records will include dates of administration, batch/serial numbers, used-by dates, and the subject (enrollment) number assigned to the study subject. At the time of return to the sponsor or alternative disposition, investigators must verify that all unused or partially used IP have been returned by the investigational sites and no remaining IP is in the investigators' possession.

The investigator or his/her delegate should complete the Study Treatment Record in the CRF.

5.9. Treatment Exposure and Compliance

All subjects will be administered LMIS 25 mg via subcutaneous injection at the study site. The administration of the IP to the subject will be under the supervision of the investigator and controlled by the clinical site personnel delegated to IP dispensing, preparation, and administration roles by PI.

5.10. Treatment for Investigational Product Overdose

The single-dose LMIS 25 mg will be carefully administered to each subject in two separate doses at 12 weeks apart by investigators or professional clinical site personnel delegated by the investigator. If any accidental overdose injection is given, the subject should be closely monitored for safety and terminated from the study.

6. STUDY PROCEDURES

This is a multi-national, multi-center, open-label, single-arm study. After providing a written informed consent, subjects with prostate cancer will be screened for baseline inclusion/exclusion criteria necessary for study eligibility. Eligible subjects will receive LMIS 25 mg from the prefilled syringes (without dilution or other mixing) in two separate subcutaneous injections given at 12 weeks apart.

Subjects who withdraw from the study prematurely for any reason during the study period will undergo the assessments listed for the final End of Study (EOS)/Early Termination (ET) visit. If a subject refuses to return for these assessments or is unable to do so, every effort should be made to contact him or a knowledgeable informant by telephone to determine his condition. Documentation of attempts to contact the subject should be recorded in the medical chart and CRF.

After LMIS 25 mg administration, subjects will be evaluated. Blood and urine samples will be collected, and other procedures will be performed as shown in **Tables 1a** and **1b**. The sign “X” indicates when the procedure should take place.

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Table 1a Study Schedule Visits 1-13

	Scrn	1 st Dose				Follow Up										2 nd 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		X ⁵								X				X		X ⁵	
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 hormone ⁷	X	X				X	X#	X	X#	X	X	X	X#	X	X	X			
Lab chemistry																			

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	Scrn	1 st Dose				Follow Up										2 nd 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).

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- 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 discretion 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 BA lab using a validated ELISA 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 BA 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 \pm 1-day window is allowed. At Visits 10 and 12 (Day 42 to Day 77), a \pm 3-day window is allowed. At Visits 13 to 16 (Day 84, for the second dose injection, week 12, to Day 87), only \pm 1-day window is allowed. At Visits 17 to 21 (Day 98 to Day 161), a \pm 3-day window is allowed. At Visits 22 (Day 168), a \pm 5-day window is allowed. At Visit 23 (Day 182), a \pm 3-day window is allowed.

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Table 1b 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.

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* 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 Day 140 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 BA lab using a validated ELISA 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 BA 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 \pm 1-day window is allowed. At Visits 10 and 12 (Day 42 to Day 77; week 6 to week 11), a \pm 3-day window is allowed. At Visits 13 to 16 (Day 84 for the second dose injection, week 12 visit, to Day 87), only \pm 1-day window is allowed. At Visits 17 to 21 (Day 98 to Day 161), a \pm 3-day window is allowed. At Visits 22 (Day 168), a \pm 5-day window is allowed. At Visit 23 (Day 182), a \pm 3-day window is allowed.

6.1. Screening Visit 1 (Day -28 ~ -1)

At the screening visit, informed consent must be obtained from the subject prior to performing any procedures related to the study and after the subject has received sufficient information about the study.

Subjects who have been screened should be listed in the screening log at study sites. Moreover, all screening procedures conducted must be documented in the CRF. If the subject fails screening or decides not to continue in the study, the primary reason should be documented in the CRF. No data will be entered into the database for screened subjects who do not meet criteria for entering the study or decide not to continue in the study. No CRF sections other than the screening section will be completed for these subjects.

Inclusion/exclusion criteria should be checked during this visit. The following study procedures will be conducted for screening assessments.

1. Record date that informed consent is signed. The following should be documented in the subject's medical chart: that they are participating in this study and informed consent has been obtained, and that a copy of the consent has been given to the subject.
2. Assign subject screening number
3. Collect demographic data
4. Record tumor history (life-time basis), medical history and medication history (record up to 6 months prior to screening visit; including blood donations and vaccinations)
5. Conduct a complete physical examination, including the measurement of body height and weight. Measure and record the vital signs including the measurement of blood pressure, heart rate, respiratory rate, and body temperature.
6. Perform Eastern Cooperative Oncology Group Performance Scale (ECOG PS) assessment
7. Perform ECG
8. Collect blood sample for analyses of:
 - Hormone: testosterone, luteinizing hormone
 - Hematology: CBC, including Hb, Hct, RBC count, WBC count, WBC differential and platelet count
 - Biochemistry: ALT, AST, ALP, total bilirubin, BUN, Serum Cr, electrolytes (K, Na, Mg, Ca and P), blood glucose, lipid profile (LDL, HDL, triglycerides)
 - PSA level
 - Glycosylated hemoglobin (HbA1c)
9. Collect urine sample for urinalysis
 - pH, specific gravity, leukocyte, erythrocyte, urine glucose, nitrate, and protein
10. Serum samples for testosterone and LH will be sent to the BA lab and Central Lab for analyses.
11. Record AE(s) if any

6.2. Visit 2 (Day 0; 1st Dose Administration)

The following study procedures will be performed at this visit:

1. Assign subject enrollment number prior to dosing.
2. Record vital signs prior to dosing.
3. Record the ECOG PS prior to dosing.
4. Perform ECG prior to dosing and at 4-hour post-dosing.
5. Collect blood sample prior to dosing for the analysis of:
 - Hematology: CBC, including Hb, Hct, RBC count, WBC count, WBC differential and platelet count
 - Biochemistry: ALT, AST, ALP, total bilirubin, BUN, Serum Cr, electrolytes (K, Na, Mg, Ca and P), blood glucose, lipid profile (LDL, HDL, triglycerides)
 - PSA level
6. Collect urine sample prior to dosing for urinalysis: pH, specific gravity, leukocyte, erythrocyte, urine glucose, nitrate, and protein.
7. Collect serum samples for determining pharmacokinetics of leuprolide mesylate and testosterone levels at pre-dose and at 2, 4, and 8 hours post-dose in the first enrolled 30 subjects. Collect serum samples at pre-dose and at 4 hours post-dose in the remaining 103 subjects for testosterone and pharmacokinetic analysis of leuprolide.
8. Collect serum samples for LH prior to dosing.
9. Assess bone pain prior to dosing.
10. Assess urinary signs and symptoms prior to dosing.
11. Record concomitant medication(s) prior to dosing and post dosing.
12. Record AE(s) prior to dosing and post dosing.
13. Administer LMIS 25 mg.
14. Investigator to assess local injection site reaction post dosing.

6.3. Visit 3 (Day 1)

The following procedures and sample collection should be performed at this visit:

1. Record vital signs.
2. Investigator to assess local injection site reaction.
3. Collect serum samples for pharmacokinetics of leuprolide mesylate.
4. Collect serum samples for testosterone and LH.
5. Assess bone pain.
6. Assess urinary signs and symptoms.
7. Record concomitant medication(s).

8. Record AE(s).

6.4. Visit 4 (Day 2)

The following procedures and sample collection should be performed at this visit:

1. Record vital signs.
2. Investigator to assess local injection site reaction.
3. Collect serum samples for pharmacokinetics of leuprolide mesylate (from the first enrolled 30 subjects only).
4. Collect serum samples for testosterone and LH (from the first enrolled 30 subjects only).
5. Record concomitant medication(s).
6. Record AE(s).

6.5. Visit 5 (Day 3)

The following procedures and sample collection should be performed at this visit:

1. Record vital signs.
2. Collect serum samples for pharmacokinetics of leuprolide mesylate.
3. Collect serum samples for testosterone and LH.
4. Record concomitant medication(s).
5. Record AE(s).

6.6. Visit 6 (Day 7 \pm 1 day, week 1)

The following procedures and sample collection should be performed at this visit:

1. Record vital signs.
2. Collect serum samples for pharmacokinetics of leuprolide mesylate (from the first enrolled 30 subjects only).
3. Collect serum samples for testosterone and LH (from the first enrolled 30 subjects only).
4. Assess bone pain.
5. Assess urinary signs and symptoms.
6. Record concomitant medication(s).
7. Record AE(s).

6.7. Visit 7 (Day 14 \pm 1 day, week 2)

The following procedures and sample collection should be performed at this visit:

1. Record vital signs.
2. Hematology: CBC, including Hb, Hct, RBC count, WBC count, WBC differential and platelet count.

3. Biochemistry: ALT, AST, ALP, total bilirubin, BUN, Serum Cr, electrolytes (K, Na, Mg, Ca, and P), blood glucose, and lipid profile (LDL, HDL, triglycerides).
4. Collect urine sample for urinalysis test: pH, specific gravity, leukocyte, erythrocyte, urine glucose, nitrate, and protein.
5. Collect serum samples for pharmacokinetics of leuprolide mesylate.
6. Collect serum samples for testosterone and LH.
7. Assess bone pain.
8. Assess urinary signs and symptoms.
9. Record concomitant medication(s).
10. Record AE(s).

6.8. Visit 8 (Day 21 \pm 1 day, week 3)

The following procedures and sample collection should be performed at this visit:

1. Record vital signs.
2. Collect serum samples for pharmacokinetics of leuprolide mesylate.
3. Collect serum samples for testosterone and LH.
4. Record concomitant medication(s).
5. Record AE(s).

6.9. Visit 9 (Day 28 \pm 1 day, week 4)

The following procedures and sample collection should be performed at this visit:

1. Record vital signs.
2. Perform ECG.
3. Collect blood sample for analysis of:
 - Hematology: CBC, including Hb, Hct, RBC count, WBC count, WBC differential and platelet count
 - Biochemistry: ALT, AST, ALP, total bilirubin, BUN, Serum Cr, electrolytes (K, Na, Mg, Ca and P), blood glucose, lipid profile (LDL, HDL, triglycerides)
 - PSA level
4. Collect serum samples for pharmacokinetics of leuprolide mesylate.
5. Collect serum samples for testosterone and LH.
6. Collect urine sample for urinalysis test:
 - pH, specific gravity, leukocyte, erythrocyte, urine glucose, nitrate, and protein
7. Assess bone pain.
8. Assess urinary signs and symptoms.

9. Record concomitant medication(s).
10. Record AE(s).

6.10. Visit 10 (Day 42 \pm 3 days, week 6-for the first enrolled 30 subjects only)

The following procedures and sample collection should be performed at this visit:

1. Record vital signs.
2. Collect serum samples for pharmacokinetics of leuprolide mesylate.
3. Collect serum samples for testosterone and LH.
4. Record concomitant medication(s).
5. Record AE(s).

6.11. Visit 11 (Day 56 \pm 3 days, week 8)

The following procedures and sample collection should be performed at this visit:

1. Record vital signs.
2. Collect serum samples for pharmacokinetics of leuprolide mesylate.
3. Collect serum samples for testosterone and LH.
4. Assess bone pain.
5. Assess urinary signs and symptoms.
6. Record concomitant medication(s).
7. Record AE(s).

6.12. Visit 12 (Day 77 \pm 3 days, week 11)

The following procedures and sample collection should be performed at this visit:

1. Record vital signs.
2. Collect serum samples for pharmacokinetics of leuprolide mesylate.
3. Collect serum samples for testosterone and LH.
4. Record concomitant medication(s).
5. Record AE(s).

6.13. Visit 13 (Day 84 \pm 1 day; 2nd Dose Administration; week 12)

The following procedures and sample collection should be performed at this visit:

1. Conduct physical examination and record vital signs (including body weight) prior to dosing.
2. Perform ECG prior to dosing and at 4-hour post-dosing.
3. Collect blood sample prior to dosing for analysis of:

- Hematology: CBC, including Hb, Hct, RBC count, WBC count, WBC differential and platelet count
 - Biochemistry: ALT, AST, ALP, total bilirubin, BUN, Serum Cr, electrolytes (K, Na, Mg, Ca, and P), blood glucose, lipid profile (LDL, HDL, triglycerides)
 - PSA level
 - Collect urine sample prior to dosing for urinalysis: pH, specific gravity, leukocyte, erythrocyte, protein, urine glucose, and nitrate.
4. Collect serum samples for pharmacokinetic analysis of leuprolide mesylate and testosterone prior to dosing and at 2, 4, and 8 hours post-dosing in the first enrolled 30 subjects. Collect serum samples prior to dosing and at 4 hours post-dosing in the remaining 103 subjects for pharmacokinetic analysis of leuprolide mesylate and testosterone.
 5. Collect serum samples for LH prior to dosing.
 6. Assess bone pain prior to dosing.
 7. Assess urinary signs and symptoms prior to dosing.
 8. Record concomitant medication(s) prior to dosing and post dosing.
 9. Record AE(s) prior to dosing and post dosing.
 10. Administer LMIS 25 mg (second administration).
 11. Investigator to assess local injection site reaction post dosing.

6.14. Visit 14 (Day 85 ± 1 day, week 13)

The following procedures and sample collection should be performed at this visit:

1. Record vital signs.
2. Collect serum samples for pharmacokinetics of leuprolide mesylate.
3. Collect serum samples for testosterone and LH.
4. Investigator to assess local injection site reaction.
5. Record concomitant medication(s).
6. Record AE(s).

6.15. Visit 15 (Day 86 ± 1 day; week 13)

The following procedures and sample collection should be performed at this visit

1. Record vital signs.
2. Collect serum samples for pharmacokinetics of leuprolide mesylate.
3. Collect serum samples for testosterone and LH.
4. Investigator to assess local injection site reaction.
5. Record concomitant medication(s).

6. Record AE(s).

6.16. Visit 16 (Day 87 \pm 1 day; week 13)

The following procedures and sample collection should be performed at this visit:

1. Record vital signs.
2. Collect serum samples for pharmacokinetics of leuprolide mesylate.
3. Collect serum samples for testosterone and LH.
4. Record concomitant medication(s).
5. Record AE(s).

6.17. Visit 17 (Day 98 \pm 3 days, week 14)

The following procedures and sample collection should be performed at this visit:

1. Record vital signs.
2. Collect serum samples for pharmacokinetics of leuprolide mesylate.
3. Collect serum samples for testosterone and LH.
4. Record concomitant medication(s).
5. Record AE(s).

6.18. Visit 18 (Day 112 \pm 3 days, week 16)

The following procedures and sample collection should be performed at this visit:

1. Record vital signs.
2. Collect serum samples for pharmacokinetics of leuprolide mesylate.
3. Collect serum samples for testosterone and LH.
4. Assess bone pain.
5. Assess urinary signs and symptoms.
6. Record concomitant medication(s).
7. Record AE(s).

6.19. Visit 19 (Day 126 \pm 3 days; week 18 for the first enrolled 30 subjects only)

The following procedures and sample collection should be performed at this visit:

1. Record vital signs.
2. Collect serum samples for pharmacokinetics of leuprolide mesylate.
3. Collect serum samples for testosterone and LH.
4. Record concomitant medication(s).

5. Record AE(s).

6.20. Visit 20 (Day 140 \pm 3 days; week 20)

The following procedures and sample collection should be performed at this visit:

1. Record vital signs.
2. Collect serum samples for pharmacokinetics of leuprolide mesylate.
3. Collect serum samples for testosterone and LH.
4. Assess bone pain.
5. Assess urinary signs and symptoms.
6. Record concomitant medication(s).
7. Record AE(s).

6.21. Visit 21 (Day 161 \pm 3 days, week 23)

The following procedures and sample collection should be performed at this visit:

1. Record vital signs.
2. Collect serum samples for pharmacokinetics of leuprolide mesylate.
3. Collect serum samples for testosterone and LH.
4. Record concomitant medication(s).
5. Record AE(s).

6.22. Visit 22 (Day 168 \pm 5 days/EOS/ ET; week 24)

The following procedures and sample collection should be performed at this visit:

1. Conduct physical examination (including body weight) and record vital signs.
2. Perform ECG.
3. Collect blood sample for analysis of the following:
 - Hematology: CBC, such as Hb, Hct, RBC count, WBC count, WBC differential and platelet count
 - Biochemistry: ALT, AST, ALP, total bilirubin, BUN, Serum Cr, electrolytes (K, Na, Mg, Ca and P), blood glucose, lipid profile (LDL, HDL, triglycerides)
 - HbA1c
 - PSA level
4. Collect urine sample for urinalysis:
 - pH, specific gravity, leukocyte, erythrocyte, protein, urine glucose, and nitrate
5. Collect serum sample for pharmacokinetics of leuprolide mesylate.
6. Collect serum samples for testosterone and LH.

7. Assess bone pain.
8. Assess urinary signs and symptoms.
9. Record concomitant medication(s).
10. Record AE(s).
11. Exit off the study (for the 103 subjects without extended PK follow up).
12. For early termination subjects, 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.

Subjects who withdraw from the study prematurely for any reason during the study period will undergo the assessments listed for the final End of Study (EOS)/Early Termination (ET) visit. If a subject refuses to return for these assessments or is unable to do so, every effort should be made to contact him or a knowledgeable informant by telephone to determine his condition. Documentation of attempts to contact the subject should be recorded in the medical chart and CRF.

6.23. Visit 23 (Day 182 \pm 3 days/PK-extended follow up; week 26)

The following procedures and sample collection should be performed **in the first enrolled 30 subjects only** at this visit:

1. Record vital signs.
2. Collect serum samples for pharmacokinetics of leuprolide mesylate.
3. Collect serum samples for testosterone.
4. Record concomitant medication(s).
5. Record AE(s).
6. Exit off the study (for the first enrolled 30 subjects only).

7. STUDY ASSESSMENTS

7.1. Screening Assessment

7.1.1. Informed consent form

The investigator or designee must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any potential AEs. Each subject will be informed that participation in the study is voluntary and that he can withdraw from participation at any time.

All subjects must provide a signed and dated informed consent at the screening visit prior to dosing LMIS 25 mg. An informed consent form approved by the Institutional Review Board (IRB), Ethics Committee (EC), and/or the applicable health authorities must be used.

7.1.2. Demographics / history

The demographic and baseline characteristics data for all subjects will be collected at the screening visit. The demographics will include date of birth, age, gender, and ethnicity.

The general medical history (including procedural and surgical history, blood donations, and vaccinations) from up to 6 months before the screening visit should be recorded at the CRF. Cancer history should be recorded in a life-time basis.

1. Tumor history should be documented, including:

- first diagnosis date,
- histological evidence,
 - TNM classification
 - Staging
- date of the last relapse or progression (if applicable)
- previous treatment of malignant disease
 - Surgery
 - Radiation therapy
 - Chemotherapy/immunotherapy
 - Cryotherapy
 - Anti-androgen therapy
 - Other modalities

Whenever possible, diagnoses should be recorded instead of symptoms.

7.1.3. Eligibility

Eligibility should be thoroughly checked by the investigator at the screening visit. See Section 4.1 and Section 4.2, Inclusion and exclusion Criteria for details.

7.1.4. ECOG performance status

ECOG performance status should be checked at the screening visit and on Day 0. The description of the ECOG performance status scale is as follows:

- 0: Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
- 1: Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
- 2: In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
- 3: In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
- 4: 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
- 5: Dead

7.2. Efficacy Assessment

Efficacy assessments will be performed based on the study schedule (Table 1a and 1b). The primary endpoint of efficacy is to determine the percentage of subjects with a serum testosterone concentration suppressed to castrate levels (≤ 50 ng/dL) on Day 28 ± 1 day (week 4) following the first injection of LMIS 25 mg, and the proportion of subjects with serum testosterone suppression (≤ 50 ng/dL) from Day 28 ± 1 day (week 4) through Day 168 ± 5 days (week 24) until the end of the study.

The proportion of subjects exhibiting post-suppression breakthrough of serum testosterone to > 50 ng/dL from Day 28 ± 1 day (week 4) through Day 168 ± 5 days (week 24) until the end of the study will also be determined.

The secondary endpoints will determine the mean acute-on-chronic changes in serum testosterone level before injection of the second dose LMIS 25 mg on Day 84 (week 12) and on Days 85, 86, 87 (week 13), and 98 (2 weeks post the second injection). The percentage of subjects observed with acute-on-chronic (surge) effect on serum testosterone and LH levels just before the second dose administration and on Day 1 to Day 3 (Days 85, 86, 87) and 14 days (Day 98) post the second injection of LMIS 25 mg will be analyzed.

The effect of LMIS 25 mg on serum LH levels and 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) by LMIS 25 mg administration will also be determined. In addition, the effects of LMIS 25 mg on the percentage of subject with PSA relapse and the percentage of subjects that achieves normal serum PSA level will be determined at the end of study.

7.2.1. Hormone level

Serum testosterone will be examined at the screening visit for eligibility (> 150 ng/dL). The screening sample of testosterone for eligibility will be sent to the Central Lab for analysis using a validated commercial assay. Thereafter, the serum testosterone can be sent to the Central Lab for analysis at the investigator's discretion. The serum testosterone will also be measured at baseline (Day 0) and at each visit for analysis at the Bioanalytical Lab. Blood samples will be collected from approximately 133 subjects in the study.

After enrollment, serum testosterone concentration in all subjects will be determined at baseline (Day 0) and at specified time points and will be sent for analysis at the Bioanalytical Lab. Blood samples for serum testosterone concentration measurement will be collected from all 133 subjects in the present study.

Serum testosterone concentrations will be measured by 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.

For a faster sample turn-around, additional serum testosterone samples can also be analyzed by a validated, commercial diagnostic method. Additional testosterone tests (by a commercial method) will be ordered at a routine frequency of no more than monthly, which is consistent with standard medical practice for leuprolide therapy for the purpose of safety monitoring. More frequent tests may be ordered by the investigators at their discretion.

Serum samples for LH concentrations will be analyzed at the BA 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.

To establish the extended serum PK/PD relationship between leuprolide and testosterone levels, blood samples for determining the 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/ET)).

Serum samples to the BA Lab will be batched and shipped periodically. Detailed procedures for blood sample collection, processing, and analysis are provided in the Laboratory Manual.

7.2.2. PSA level

The PSA tumor marker will be assessed at specified visit as one of the endpoint assessments in all subjects. Blood samples will be collected at the screening visit, Day 0 (prior to dosing), Day 28 ± 1 day (week 4), Day 84 ± 1 (prior to dosing, week 12), and Day 168 ± 5 days (week 24, EOS/ET). All collected blood samples will be sent to the central laboratory for analysis. More frequent tests may be ordered by the investigators at their discretion.

Detailed procedures for blood sample collection, processing, and analysis are provided in the Laboratory Manual.

7.3. Safety Assessment

7.3.1. Physical examinations and vital signs

Physical examination will be performed in all subjects at the screening visit, Day 84 ± 1 day (week 12), and Day 168 ± 5 days (week 24, EOS/ET), by standard physical examination including general appearance, skin, eyes, ear/nose/throat (ENT), head and neck, heart, chest and lungs, abdomen, extremities, lymph nodes, musculoskeletal, neurological, and other body systems if applicable for describing the status of the subject's health.

Changed in physical examinations with clinical significance compared to baseline by principal investigator's judgment will be analyzed.

Height in centimeters (cm) will be measured while the subject is standing after removing his shoes, and the measurement will only be conducted at screening visit. Body weight will be measured at the screening visit, Day 84 (week 12), and Day 168 ± 5 (week 24, EOS/ET) to the nearest 0.1 kilogram (kg) or pound (lb.) in indoor clothing without shoes.

Vital signs will be measured at each visit, including resting blood pressures, heart rate, respiratory rate, and body temperature.

7.3.2. Local injection site reaction assessment

The specific injection location chosen should be an area with sufficient soft or loose subcutaneous tissue, for example, the upper- or mid-abdominal area. Local AEs have been reported in Eligard[®] studies. The local AEs typically seen with subcutaneously injected products include: transient burning, stinging, and pruritus at the injection site and are typically of mild intensity and brief duration.

The local injection site reaction assessments should include itchiness, erythema, burning and stinging sensation. Assessments will be carried out after investigational product administration and recorded on Day 0, Day 1, Day 2, Day 84, Day 85, and Day 86.

Any local site injection reactions will be captured under AE reporting at the next follow up visit if last longer than 3 days with any severity post LMIS 25 mg administration. The grading for the assessment of local injection reaction is provided in [Table 2](#).

Table 2 Grading of local injection reaction

Grade	Burning/Stinging	Pruritus	Erythema
0 (None)	No stinging / burning	No pruritus	No detectable erythema, skin of normal color
1 (Mild)	Slight warm, tingling sensation; not really bothersome	Occasional, slight itching / scratching	Slight pinkness present
2 (Moderate)	Definite warm, tingling sensation that is somewhat bothersome	Constant or intermittent itching / scratching which is not disturbing sleep	Definite redness, easily recognized
3 (Severe)	Hot, tingling / stinging sensation that has caused definite discomfort	Bothersome itching /scratching which is disturbing sleep	Intense redness

7.3.3. Hematological / biochemistry examinations

The safety profile of LMIS 25 mg will be assessed using lab test including hematological and biological examinations by collecting blood samples from all subjects.

Hematological tests will include complete blood count (CBC): hemoglobin (Hb), hematocrit (Hct), red blood cells (RBC), white blood cells (WBC), WBC differential (neutrophils, eosinophils, basophils, lymphocytes, and monocytes), platelet counts, and HbA1c. Biochemistry tests will include ALT, AST, ALP, total bilirubin, BUN, Serum Cr, electrolytes (K, Na, Mg, Ca and P), blood glucose and lipid profile (LDL, HDL, triglycerides).

Laboratory tests, except for the HbA1c, will be performed during the screening visit and on Day 0 (prior to dosing), Day 14 ± 1 day (week 2), Day 28 ± 1 day (week 4), Day 84 ± 1 (prior to dosing, week 12), and Day 168 ± 5 days (week 24, EOS/ET).

The HbA1c will be performed at the screening visit and at the final visit (Day 168, week 24, or End of Study Visit/Early termination).

Blood samples for laboratory tests will be collected and will be sent to the Central Laboratory for analyses.

7.3.4. Urinalysis

Urinalysis will be collected from all subjects to assess the safety profile of LMIS 25 mg. The urinalyses will include urine pH, specific gravity, leukocyte, erythrocyte, urine glucose, nitrate, and protein.

The urinalysis will be performed at screening, Day 0 (prior to dosing), Day 14 \pm 1 day (week 2), Day 28 \pm 1 day (week 4), Day 84 \pm 1 (prior to dosing, week 12), and Day 168 \pm 5 days (week 24, EOS/ET).

Urine samples will be collected and sent to the Central Laboratory for analyses.

7.3.5. ECG

ECG examination will be performed by standard 12-lead at the screening visit for eligibility and on Day 0 (prior to dosing and at 4-hour post-dosing), Day 28 \pm 1 day (week 4), Day 84 \pm 1 (prior to dosing and at 4-hour post-dosing, week 12), and Day 168 \pm 5 (week 24, EOS/ET).

7.3.6. Bone pain

Pain is a common problem for men with prostate cancer, but not all men will have pain. The most common cause of pain is because cancer has spread to the bones, but even that more than 25% of men don't have any pain. If cancer has spread to several other body organs, men often only have pain in a few of these organs.

Bone pain caused by cancer which has spread to the bones has a very specific feeling. Some subjects describe it as feeling similar to a toothache but in the bones, or like a dull aching or stabbing. Bone pain will be assessed by subject visual assessment scales (VAS) ranging from 1 (no pain) to 10 (worst possible pain) (see [Appendix II](#)), and will be evaluated at baseline (Day 0, pre dose), Day 1, Day 7 \pm 1 day (week 1), Day 14 \pm 1 day (week 2), Day 28 \pm 1 day (week 4), Day 56 \pm 3 days (week 8), Day 84 \pm 1 day (pre dose, week 12), Day 112 \pm 3 days (week 16), Day 140 \pm 3 days (week 20), and Day 168 \pm 5 days (week 24, EOS/ET).

7.3.7. Urinary signs and symptoms

Urinary signs and symptoms will be assessed using the International Prostate Symptom Score (I-PSS) including 7 questions (See [Appendix III](#)). Based on the total score from answering the 7 questions, the urinary symptom can be assessed as: 1-7 (Mild), 8-19 (Moderate), 20-35 (Severe). Urinary signs and symptoms will be evaluated at baseline (Day 0, pre dose), Day 1, Day 7 \pm 1 day (week 1), Day 14 \pm 1 day (week 2), Day 28 \pm 1 day (week 4), Day 56 \pm 3 days (week 8), Day 84 \pm 1 day (pre dose, week 12), Day 112 \pm 3 days (week 16), Day 140 \pm 3 days (week 20), and Day 168 \pm 5 days (week 24).

7.3.8. Adverse events

Subjects will be asked to report AEs voluntarily. The investigator will also question and examine the subjects to identify any AEs at each visit (including screening visit). See [Section 9.1](#) and [Section 9.2](#) for detailed information on AEs.

7.4. Pharmacokinetics Assessment

7.4.1. Pharmacokinetic assessments of LMIS 25 mg

Pharmacokinetic assessments of LMIS 25 mg will be conducted by measuring the serum leuprolide concentration using a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) method.

To evaluate the sustained castration testosterone level after two doses of LMIS 25 mg injections, the PK/PD analysis (serum testosterone and leuprolide levels) in the first enrolled 30 subjects on Day 182 (week 26) will also be determined. This additional sampling is meant to assess the flexibility of the time period between doses during routine use of LMIS 25 mg and these 30 subjects will be considered as the subset population for PK analysis. Thus, the first enrolled 30 subjects will have more intensive sampling to establish the extended PK profile of serum leuprolide concentrations by collecting blood samples on Day 0 (prior to the first dose of LMIS 25 mg, and at 2, 4, and 8 hours post-dose), Days 1, 2, 3, 7, 14, 21, 28, 42, 56, 77, 84 (week 12: prior to the second dose and at 2, 4, and 8 hours post the second dose), 85, 86, 87, 98, 112, 126, 140, 161, 168 (week 24), and 182 (week 26/ EOS/ET).

The remaining approximately 103 subject will have blood samples collected for determining the serum leuprolide concentrations 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 (week 12: prior to the second dose and 4 hours post dose), 85, 86, 87, 98, 112, 140, 161, and 168 (week 24/EOS/ET).

All blood samples will be collected from subjects by direct venipuncture (approximately 6 mL blood per sample). With regard to the time window for blood sample collection, 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, week 12 visit, for the second dose injection, 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 Visit 22 (Day 168/week 24), a ± 5 -day window is allowed. At Visit 23 (Day 182/week 26), a ± 3 -day window is allowed.

All PK/PD blood samples will be centrifuged for serum at $1000 \times g$ for 15 minutes as soon as possible after collection. The samples will be maintained in an ice bath throughout sample collection and preparation. Please see Laboratory Manual for complete instructions.

All samples will be packed in dry ice and sent to the analytical facility. All shipments will be accompanied by an inventory list with other appropriate documents. Additional details of sample collection, handling, and processing are outlined in the Laboratory Manual.

7.4.2. Serum sample analysis for Leuprolide Mesylate

Serum samples collected on the above specified time points will be analyzed for leuprolide mesylate using a validated LC/MS/MS method.

7.4.3. Pharmacokinetic analysis of Leuprolide Mesylate

The pharmacokinetic profile of leuprolide mesylate, including C_{max} , T_{max} , C_{week4} , C_{week12} , $AUC_{0-week4}$, $AUC_{0-week12}$, $C_{avg(0-week12)}$ will be determined after each dose using Phoenix WinNonlin[®] with non-compartmental approaches.

8. CONCOMITANT TREATMENT

All concomitant medications, both permitted and proscribed, and significant non-drug therapies, such as surgery, blood transfusions and physical therapy, administered after the subject begins participation in this study will be recorded in the source documents and in the concomitant treatment log in the CRF. Those records will include generic name / trade names (allowed for combination medication only), medical indication, total daily dose, route of administration, and start and end dates of treatment.

Treatments within 6 months prior to the first administration of study drug will be recorded in the CRF. Moreover, all concomitant medications administered for the treatment of an AE must be recorded.

8.1. Permitted Treatment

1. Bisphosphonates will be permitted during the study.
2. Denosumab will be permitted during the study.
3. Supplementation of vitamin D and calcium will be allowed during the study if, in the Investigator's opinion, it is needed for the subject's health.
4. Plain, over-the-counter, multi-vitamins will be permitted during the study.
5. Glucocorticosteroids will be allowed if being used as a replacement therapy.
6. Pain medication will be allowed if it is an over-the counter or prescription medication and prescribed by a physician and as described in [Appendix IV](#).
7. Oral hypoglycemics will be allowed for control of Type II diabetes.
8. Radiation for pain control will be allowed during the study.

Any use of concomitant treatment must be recorded in the CRF.

8.2. Prohibited Treatment

The following medications are prohibited during the study period (from screening visit to EOS):

1. Other gonadotropin-releasing hormones
2. Other chemotherapy, immunotherapy, cryotherapy, or radiotherapy for treatment of prostate cancer
3. Any OTC medication other than those listed in the Concomitant Treatment section.
4. Dietary supplements, herbal supplements, or herbal tea.
5. Insulin
6. Anti-androgens
7. 5-alpha reductase inhibitors
8. Systemic corticosteroids > 10 mg/d

Subjects who have received these prohibited treatments will be withdrawn from the study.

8.3. Rescue Medication and Treatment

In the event of emergency, the investigator will perform clinical life-support procedures according to the individual situation.

9. SAFETY MONITORING

9.1. Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. However, abnormal laboratory values or changes are not automatically reported as an AE if they are not clinically significant. They will only be recorded as AEs if a therapeutic action is needed or the investigator judges them to be clinically significant.

The occurrence of AEs should be sought by non-directive questioning of the subject at each visit and/or telephone follow-up during the study. AEs also may be detected when they are volunteered by the subject during or between visits or through physical examination, vital sign measurement, laboratory test or other assessments. All AEs must be recorded on the Adverse Events CRF with the following information:

1. AE term and description
2. Duration (onset and resolution dates or if continuing at final exam)
3. Severity grade (mild, moderate, severe, life-threatening, death)
4. Whether the AE constitutes an SAE
5. Relationship to the study drug (definite/ possible/ unrelated)
6. Action taken and treatment required
7. Outcome (recovered/resolved, recovered/resolved with sequelae, recovering/resolving, not recovered/not resolved, fetal)

9.1.1. The severity grade of AEs

The investigator will make an assessment of the maximum intensity that occurred over the duration of the event for all AEs reported during the study period using CTCAE version 4. The assessment will be based on the investigator's clinical judgment. The severity of each AE and SAE recorded in the CRF should be assigned to one of the categories as described in [Table 3](#).

Table 3 Intensity Scales of Adverse Events

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

ADL: Activities of Daily Living; AE: Adverse Events

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

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

9.1.2. The relationship to study drug

The investigator will make an assessment of the relationship between the study drug and the occurrence of each AE/SAE. The reasonable possibility of causation will be determined based on the investigator's clinical judgment. The causality should be considered as one of the categories described in [Table 4](#).

The AEs should be followed until resolution or until the event is considered stable. Both regular return visits and telephone contacts may be required.

Table 4 The Relationship between Adverse Events and Occurrence

Relationship	Description
Definite	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Unrelated	A clinical event, including laboratory test abnormality, which is clearly not related to drug administration.

9.2. Serious Adverse Events

A serious adverse event (SAE) is any experience that suggests a significant hazard, contraindication, side effect or precaution. With respect to human clinical experience, this includes any event which:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of hospitalization, unless hospitalization is for:
 - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
 - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
 - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
 - social reasons and respite care in the absence of any deterioration in the subject's general condition
- results in persistent of significant disability / incapacity, or
- is a congenital anomaly / birth defect,
- is a significant or important medical event that, based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

9.3. Serious Adverse Events Reporting Requirement and Emergency Procedures

Any AE which is fatal or life threatening that occurs during the study must be reported promptly (within 24 hours) to the sponsor (Foresee) or QPS, irrespective of whether it is related to the use of investigational product. If reported to QPS, QPS will inform the sponsor on the same day or at the earliest possible time. At the time of the reporting, the following information should be provided if possible: study center, subject enrollment number, dose cohort during which the event occurred, a description of the event, date of onset and current status, outcome, action taken with the investigational drug, the reason why the event is classified as serious, and the Investigator's current assessment of the association between the event and investigational drug.

Within the required timeframe, the investigator must provide further information on each SAE to Foresee/QPS, and QPS will assist the investigator in submitting the SAE to the appropriate IRB/EC, ADR reporting center, and Foresee. The SAE/SUSAR (Suspected Unexpected Serious Adverse Reaction) will be reported to both competent authorities and relevant IRBs/IECs in accordance with the regulatory requirements of the country in which the SAE occurred.

Each recurrent episode, complication, or progression of the initial SAE should be reported as a follow-up to the original episode within 24 hours of the investigator's receiving the follow-up

information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previous one should be reported separately as a new event.

9.4. Pregnancies

All subjects will be instructed to use adequate contraceptive precautions until the end of study. When pregnancy of a subject's spouse has been discovered, the pregnancy must be reported to sponsor/Contract Research Organization (CRO). The pregnancy outcomes, including spontaneous or voluntary termination, details of the pregnancy and birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, will be followed. The infant's medical record should be followed up to 1 year after birth.

10. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

10.1. Sample Size

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).

10.2. Analysis Population

In this study, there will be three populations, including intention-to treat (ITT), per protocol (PP), and safety 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 populations for analysis applied in this study are defined as follows:

1. The Intention-To-Treat (ITT) population will consist of any subject receiving at least one dose of LMIS 25 mg.
2. 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.
3. The safety population will consist of any subject receiving a dose of LMIS 25 mg.

10.3. Analysis Method

For descriptive statistics, continuous variables will be presented as number of observations, mean, standard deviation (SD), median, range, Hodges-Lehmann estimator, and 95% CI.

Categorical variables will be presented by frequency and percentage.

Changes from baseline will be tested by paired t-test or Wilcoxon signed-rank test for continuous variables using a significance level of 0.05.

10.4. Efficacy Analysis

The efficacy analysis will be based on the following endpoints assessments in both ITT and PP populations.

10.4.1. Analysis of primary endpoint

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

The percentage of subjects with a serum testosterone concentration suppressed to castrate levels (≤ 50 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 approximation to a Binomial distribution. The percentage of subjects with testosterone suppression (≤ 50 ng/dL) from Day 28 (week 4) through Day 168 ± 5 days (week 24) will be analyzed using the Kaplan-Meier approach.

Insufficient testosterone suppression is defined as suppression that does not occur by Day 28 (week 4) or occurrence of a testosterone level >50 ng/dL between Day 28 (week 4) and Day 168 (week 24).

The following efficacy analyses will be provided in detail in the statistical analysis plan:

- The proportion of subjects with testosterone suppression (≤ 50 ng/dL) from Day 28 (week 4) through Day 168 ± 5 days (week 24)
- Subjects exhibiting post-suppression breakthrough of serum testosterone to >50 ng/dL
- Time to event: A subject with a testosterone level > 50 ng/dL between Days 28 and 168 is considered to have an event.

To accommodate drop-out and missing values, the data censoring rules is shown in [Table 5](#).

10.4.2. Analysis of secondary endpoints

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 (Day 98, week 14)

The mean acute-on-chronic changes in serum testosterone concentration will be summarized by descriptive statistics. The change from baseline will be summarized descriptively and a paired t-test or Wilcoxon signed-rank test will be used, data significance level of 0.05.

- 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 during the study will be summarized as descriptive statistics. The mean acute-on-chronic changes in LH level from after the 2nd injection of LMIS 25 mg will be summarized descriptively. The change from baseline will be summarized descriptively and a paired t-test or Wilcoxon signed-rank test will be used, data significance level of 0.05.

- 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). A post hoc analysis will be performed to determine the incidence of PSA recurrence.

The incidence of PSA relapse is defined as after achieving serum PSA level ≤ 4 ng/mL post LMIS 25 mg injection but with an increase in serum PSA $> 50\%$ compared with nadir will be presented as a count, percentage, and 95% CI.

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

The number of subjects achieving normal serum PSA level (<4 ng/dL) on Day 168 ± 5 days (week 24) will be presented as a count, percentage, and 95% CI.

- The percentage of subjects achieving 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 an enhanced serum testosterone suppression to ≤ 20 ng/dL by Day 28 ± 1 day (week 4) and Day 168 ± 5 days (week 24) will be analyzed using a standard large sample normal approximation to a Binomial distribution.

Table 5 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

10.5. Safety Analysis

The safety analysis of LMIS 25 mg will be based on the following safety assessments:

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

The analysis of AEs will be tabulated by system organ class (SOC) and preferred terms according to the current MedDRA dictionary. Preferred terms will be used and presented as standardized tabulations by frequency and incidence rates. AE incidence rates will be analyzed by severity and relationship to study drug. Any AE leading to death, discontinuation from the study, or change of dose will be listed as per regulations. If any SAE occurs, a summary of the SAEs will be described and listed.

- Assessment of injection site reaction

The local injection site reaction will be summarized descriptively.

- Change in bone pain measurement (by Visual Analogue Scale [VAS] scale)
- Change in urinary signs and symptoms and the total score between baseline (Day 0) and Day 168 \pm 5 (days, week 24) (by the International Prostate Symptom Score, I-PSS sheet)

The summary results of bone pain measurement (by VAS scale) at baseline (Day 0), end of study visit (EOS/ET, Day 168 \pm 5 days, week 24), and the change from baseline will be summarized descriptively. The change from baseline to EOS visit will be tested by paired t-test or Wilcoxon signed-rank test at a significance level of 0.05. The urinary signs and symptoms (by the International Prostate Symptom Score, I-PSS, sheet) at baseline (Day 0) and EOS/ET visit (Day 168 \pm 5 days, week 24) will be summarized descriptively

- Change in vital signs (BP, HR, RR, weight)
- Change in physical examinations with clinical significance compared to baseline by principal investigator's judgment

The summary results of change in physical examinations with clinical significance vital signs (BP, HR, RR) and weight at baseline (Day 0), EOS/ET Visit (Day 168 \pm 5 days, week 24), and the change from baseline will be summarized descriptively. Also the change from baseline (Day 0) to the EOS/ET Visit (Day 168 \pm 5 days, week 24), will be tested by paired t-test or Wilcoxon signed-rank test at a significance level of 0.05. The transition matrix of physical examination and change in vital signs will be summarized.

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

The summary results of laboratory data at baseline (Day 0) and the EOS Visit (Day 168 \pm 5 days, week 24) and change from baseline (Day 0) to the EOS/ET Visit (Day 168 \pm 5 days, week 24) will be summarized by descriptive statistics and paired t-test or Wilcoxon signed-rank test and will be used at a significance level of 0.05. The transition matrix of change in laboratory data between baseline (Day 0) and the EOS/ET Visit (Day 168 \pm 5 days, week 24) will be summarized.

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

The summary results of 12-lead resting ECG at baseline (Day 0) and the EOS/ET Visit (Day 168 \pm 5 days, week 24) will be summarized descriptively. The transition matrix for ECGs will be summarized.

10.6. Pharmacokinetics Analysis

The pharmacokinetic profile of leuprolide mesylate will be determined in a sub-set of subjects (first 30 subjects enrolled) through more intensive PK sampling. PK analyses will also be conducted for other subjects as well and results will be used as supporting data.

The serum pharmacokinetic profile of leuprolide following 2 subcutaneous injections of LMIS 25 mg given 12 weeks apart will be determined from baseline (Day 0) to Day 168 (week 24). The serum pharmacokinetic/pharmacodynamics levels of leuprolide, testosterone, and LH will be followed for additional 2 weeks post Day 168 (Day 182, week 26) in the first enrolled 30 subjects to evaluate the PK/PD relationship between LMIS 25 mg and the sustained castration testosterone level after two doses of LMIS 25 mg injections.

The PK parameters of leuprolide will be determined during the study period, including C_{max} , T_{max} , C_{week4} , C_{week12} , $AUC_{0-week4}$, $AUC_{0-week12}$, $C_{avg(0-12\text{ week})}$ after each dose. The Day 182 (week 26) leuprolide serum concentration data will also be assessed in the first enrolled 30 subjects (PK sub-set). The pharmacokinetic parameters of leuprolide ([Table 6](#)) will be calculated from the serum concentrations collected during the study. Phoenix WinNonlin[®] will be used for the pharmacokinetic analyses using a non-compartmental analysis model.

Table 6 Pharmacokinetic analysis of leuprolide mesylate in all subjects

Term	Definition
C_{max}	Maximum observed serum concentration
T_{max}	Time to the maximum serum concentration
C_{week4}	Observed serum concentration at 4 weeks (approximately 28 days) post dosing
C_{month3}	Observed serum concentration at 12 weeks (approximately 84 days) post dosing
$AUC_{0-week4}$	Area under the concentration-time curve calculated using the linear up/log down trapezoidal method from time zero to 4 weeks (approximately 28 days) post dosing
$AUC_{0-week12}$	Area under the concentration-time curve calculated using the linear up/log down trapezoidal method from time zero to week 12 (approximately 84 days) post dosing
$C_{avg(0-week12)}$	Mean serum concentration within 12 weeks (approximately 84 days) post dosing

avg: average; max: maximum;

Statistical analyses will be performed for serum leuprolide using the SAS[®] system for Windows or Phoenix WinNonlin[®]. Arithmetic means, SD, and coefficients of variation will be calculated for the pharmacokinetic parameters listed above.

For the pharmacokinetic assessment of leuprolide, all measured values below quantifiable limit (BQL) will be set to zero for all pharmacokinetic and statistical evaluation. Any missing samples will be reported as 'NS' and will not be included for pharmacokinetic or statistical analysis.

10.7. Handling of Missing Values

For handling missing data related to a safety or efficacy endpoints, no missing data method will be performed. 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 the day of last measurement
3. Any subject having more than one missing testosterone values will be censored on the day with the 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).

11. STUDY ADMINISTRATIVE STRUCTURE

11.1. Ethical Conduct of the Study

The study will be performed in accordance with the protocol, ICH Harmonized Tripartite Guidelines for Good Clinical Practice (GCP) and applicable local regulations.

The US FDA has eliminated all reference to the Declaration of Helsinki since 2006 and uses the ICH Guidelines for GCP in addition to 21 CFR 50 and 21 CFR 56. The study will be conducted in compliance with 21 CFR 312 and 54 (financial disclosure). For the US sites those regulatory documents are considered primary.

In general, and for other regions of the world, the Declaration of Helsinki 7th revision (2013) and/or the ICH Guidelines for GCPs will be considered primary documents for this study, unless local or regional regulatory preferences dictate otherwise.

11.2. Institutional Review Board (IRB) / Ethics Committee (EC)

The principal investigator will provide the IRB or EC with all appropriate essential documents, including the protocol and the informed consent document. The trial will not be initiated until appropriate IRB or EC approval of the appropriate essential documents is received by the investigator and the sponsor (Foresee). In addition, the investigator is responsible for reporting SAEs, as defined in the protocol, to the IRB/IEC at each investigational site/study center according to the applicable, local regulations.

11.3. Informed Consent Process and Subject Information

A properly executed written informed consent in the applicable local language will be obtained from each subject prior to the subject's entrance into the trial and prior to performance of any procedure that involves risk to the subject.

Each investigator will provide a copy of the IRB-approved informed consent to every subject and a signed copy shall be maintained in the subject's record file. The basic elements will be incorporated into the informed consent according to the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), 21 CFR 50 and 21 CFR 56 (in the US) and in accordance with the Declaration of Helsinki 7th revision (2013) in areas of the world where this is recognized. The information will include the experimental setting, trial objectives, possible benefits, side effects and dangers of participation in the trial, currently available alternative procedures or treatment regimens, the rights and responsibilities of the trial subject, and other information that is relevant to the subject's decision to participate.

12. INSURANCE AND INDEMNITY

All subjects will be insured by Foresee against complications of any kind which are directly caused by the administration of the investigational drug or the study procedures. Information regarding insurance and indemnity will be provided to the investigators by the sponsor prior to the initiation of this trial.

13. SOURCES DOCUMENTS

To enable evaluations and/or audits from health regulatory authorities, QPS or Foresee, the investigator will agree to keep secure records that include the identity of participating subjects, original signed Informed Consent Forms (ICFs), copies of CRFs and detailed records of medication disposition and study procedures. The principal investigator must maintain all documentation relating to the study according to the national law or regulations for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. The investigator and Foresee will retain the subjects' identification and all trial-related documents according to the appropriate regulatory authorities and the requirements of the sponsor. No records will be destroyed by the clinical sites without the written consent from Foresee Pharmaceuticals.

All information provided to the investigator by the sponsor, including pre-clinical data, the protocols and any other information should be kept confidential and confined to the clinical personnel involved in conducting the study or authorized representatives of appropriate health/regulatory authorities. Identity, hospital records, and site records of each subject will also kept confidential except for authorized personnel.

14. CASE REPORT FORM

It is Foresee's policy that all study data must be verifiable to the source data, which necessitates access to all original recordings, laboratory reports, and subjects' records. The investigator must agree to allow access to the subjects' records and source data by Foresee, QPS, the IRB/EC and Health Authorities personnel. The subjects must also agree to allow access to the subjects' medical records. Subjects will provide written consent before this action is taken. Correction to data on source data may be made only by putting a line through the incorrect data and writing the correct values, allowing the original text to remain legible. Each correction must be initialed and dated by the person making the change. If corrections are made after review and signature by the investigator, the investigator must be made aware of the changes.

15. CONTROL AND ASSURANCE OF STUDY QUALITY

15.1. Assignment of Site Monitor

All aspects of the study will be conducted under ICH GCP and FDA guidelines. Qualified individuals designated and approved by QPS and the sponsor will monitor the study. Monitoring will be conducted according to GCP and standard operating procedures for compliance with applicable government regulations. The investigator will agree to allow these monitors access to the study and medical files for the subjects, the clinical supplies, the IP dispensation documents, and the test drug storage areas and, if requested, agree to assist the monitors.

15.2. Data Quality Assurance

The study will be monitored by regular site visits and telephone calls to the investigator by QPS, QPS contractors, and/or Foresee representatives as outlined in the Monitoring Plan. During the site visits, the monitor will review original subject records, drug accountability records, and the study file. The monitor will also meet with the investigator to discuss the study status and any issues.

15.3. Audits and Inspections

Auditors, authorized representatives from Foresee Pharmaceuticals, an IRB or an IEC; and/or inspectors from a regulatory authority may visit the site to perform audits or inspections. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The investigator should contact Foresee Pharmaceuticals or QPS, LLC immediately if contacted by a regulatory agency for an inspection or by IRB/IEC for an audit.

16. PROTOCOL DEVIATION / VIOLATION

All deviations from the protocol should be reported to QPS. This includes, but is not limited to, the following:

1. Subjects who entered the study but did not satisfy all entry criteria;
2. Subjects who satisfied the criteria for one or more of the withdrawal reasons during the study but were not withdrawn;
3. Subjects who received the wrong treatment or incorrect dose;
4. Subjects who received concomitant treatment in an incorrect manner or who received a non-approved concomitant treatment.
5. Subjects who missed the sample collection for efficacy assessment on the scheduled visit

Examples include subject noncompliance with medication, surreptitious use of medications prohibited by the protocol, inability, or unwillingness to accurately report AEs or concomitant medication use. Additionally, exceptions or deviations that could conceivably affect the collection or interpretation of the data related to safety or efficacy assessments should also be reported.

17. PROTOCOL AMENDMENTS

Only Foresee may modify the protocol. Amendments to the protocol will only be made after consultation and agreement between Foresee, QPS, and the investigator. All amendments that have an impact on subject risk, safety, or the study objectives, or require revision of the informed consent document, must receive approval from the appropriate IRB/EC prior to its implementation.

18. COMPLETION OF STUDY

This study will be completed after all subjects completed the end of the 6-month visit (Day 168/week 24 or Day 182/ week 26 in the first enrolled 30 subjects).

19. TERMINATION OF STUDY

Foresee Pharmaceuticals reserves the right to discontinue this trial at any time. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB/IEC and will provide the reason(s) for the termination or suspension. Foresee Pharmaceuticals or the designated representative will promptly inform the regulatory authority.

20. RETENTION OF RECORDS AND CONFIDENTIALITY

Clinical investigators are responsible for maintaining study information (e.g., the original signed Informed Consent, copies of CRFs, and detailed records of medication disposition) pertaining to the subject's identity in a confidential manner. If the need arises, only Foresee, QPS, or appropriate regulatory/health authorities will have access to this information.

21. USE OF INFORMATION AND PUBLICATION

No part of the study protocol or its amendments, nor any information given by Foresee or QPS to the investigators for the purpose of evaluating and/or performing the study, shall be disclosed to any third party without prior written consent from Foresee. The investigator is obliged to provide Foresee and QPS with copies of all data derived from the study. Except for when required by law, only Foresee has the sole right to disclose the study information to other physicians and regulatory agencies.

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APPENDIX I

DECLARATION OF HELSINKI

World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)

55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Introduction

The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the subject's interest when providing medical care which might have the effect of weakening the physical and mental condition of the subject."

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

Basic Principle for All Medical Research

It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the Investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any SAEs. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily

managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

The subjects must be volunteers and informed participants in the research project.

The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the subject's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results

should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

Additional Principles for Medical Research Combined With Medical Care

The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the subjects who are research subjects.

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. (See footnote*)

At the conclusion of the study, every subject entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

The physician should fully inform the subject which aspects of the care are related to the research. The refusal of a subject to participate in a study must never interfere with the subject-physician relationship.

In the treatment of a subject, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the subject, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

****FOOTNOTE:***

Note of Clarification on Paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the subjects who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

APPENDIX II

Visual Analogue Scale

(VAS)

The visual analog scale (VAS) is a unidimensional measure of pain intensity in adults. For this scale, subjects indicate their current level of pain along a 10 cm line with 'no pain' at one end and 'worst pain imaginable' at the other. The VAS score is determined by measuring the line in centimeters from the left end to the point that the subject marks his degree of pain.

Instructions for producing a VAS Card:

- Print or photocopy the diagrams to ensure that the line is exactly 10 cm in length.
- Advise the subject marks on the line to the point that they feel represents their perception of their current painful states.

Subject Name: _____ Enrollment number: _____

Date completed (dd-mon-year): _____ Visit number: _____



APPENDIX III**International Prostate Symptom Score (I-PSS) (1/2)****Subject Name:** _____ **Enrollment number:** _____**Date completed (dd-mon-year):** _____ **Visit number:** _____

Please circle one number in the following questions.

In the past month	Not at All	Less Than 1 in 5 Times	Less than Half the Time	About Half the Time	More Than Half The Time	Almost Always
1. Incomplete Emptying: how often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5
2. Frequency: how often have you had to urinate again in less than 2 hours after you finished urinating?	0	1	2	3	4	5
3. Intermittency: how often have you found you stopped and started again several times when you urinated	0	1	2	3	4	5
4. Urgency: how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Weak Stream: how often have you had a weak urinary stream?	0	1	2	3	4	5
6. Straining: how often have you had to strain to start urination?	0	1	2	3	4	5
	None	1 Time	2 Times	3 Times	4 Times	5 or More Times
7. Nocturia: how many times did you typically get up to urinate during the night?	0	1	2	3	4	5
Total I-PSS Score (Add number from question 1 to 7)						

International Prostate Symptom Score (I-PSS) (2/2)**Quality of Life Due to Urinary Symptoms:****Subject Name:** _____ **Enrollment number:** _____**Date completed (dd-mon-year):** _____ **Visit number:** _____

Circle One Number in the Next Row	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Name of CRC: _____ **Signature of CRC:** _____**Date:** _____

OR

Name of PI: _____ **Signature of PI:** _____**Date:** _____

PI: Principal investigator

!Please keep this questionnaire in the subject folder!

APPENDIX IV

Pain in cancer subjects within the trial should be treated properly and sufficiently. The list of allowed medication in the three-step pain treatment, including recommended dosage, is attached. OTC medicines are allowed if they are included on the below list. Herbal products are prohibited. Treatment with NSAIDs (non-steroidal anti-inflammatory drugs) should be covered by parallel application of potent proton pump inhibitors (e.g. Omeprazole) in sufficient dosage according to the product's package insert or the SPC (Summary of Product Characteristics-EU).

List of the allowed medication in alphabetical order follows:

Acetaminophen (paracetamol), Aspirin, Buprenorphine, Butorphanol, Celecoxib, Codeine, Diclofenac, Diflunisal, Dihydrocodeine, Etodolac, Fenoprofen, Fentanyl buccal tablet, Fentanyl transdermal system, Fentanyl citrate oral transmucosal (OTFC), Flurbiprofen, Hydrocodone, Hydromorphone, Choline magnesium trisalicylate, Ibuprofen, Indomethacin, Ketoprofen, Ketorolac, Levorphanol, Meclofenamic acid, Mefenamic acid, Meloxicam, Meperidine (Pethidine), Methadone, Morphine, Morphine (Modified-release), Nabumetone, Nalbuphine, Naproxen, Naproxen sodium, Oxaprozin, Oxycodone, Oxycodone (Modified-release), Oxymorphone, Oxymorphone (Modified-release), Pentazocine, Phenylbutazone, Piroxicam, Propoxyphene (HCl and napsylate), Salsalate, Sulindac, Tolmetin, Tramadol.

Three-Step Pain Treatment for Foresee FP01C-17-001 Clinical Trial

Adjusted according to guidelines:

Russell K. Portenoy: Three-step analgesic ladder for management of cancer pain; Dept. of Pain Medicine and Palliative care, Beth Israel Medical Center, New York, New York

ALLOWED MEDICATIONS FOR PAIN, DOSAGES AND SCHEDULE:

First Step

NONOPIOID ANALGESICS FOR MILD TO MODERATE PAIN

Class	Generic Name	Dosing Schedule	Recommended Starting Dose mg/d*	Maximum
	Salsalate	q12h	1,500 x 1, then 1,000 q12h	4,000
Propionic acids §	Fenoprofen+	q4-6h	800	3,200
	Flurbiprofen	q8-12h	100	300
	Ibuprofen+	q4-8h	1,200	3,200

Class	Generic Name	Dosing Schedule	Recommended Starting Dose mg/d*	Maximum
	Ketoprofen+	q6-8h	150	300
	Naproxen+	q12h	500	1,000
	Naproxen sodium+	q12h	550	1,100
	Oxaprozin	q24h	600	1,800
Acetic acids	Diclofenac	q6h	150	200
	Etodolac+	q6-8h	600	1,200
	Indomethacin	q8-12h	75	200
	Ketorolac+	q6h	15-30 q6h I.V., IM 10 q6h PO	120 I.V., IM 40 PO
	Sulindac	q12h	300	400
	Tolmetin	q6-8h	600	1,800
Naphthylalkanone	Nabumetone	q24h	1,000	2,000
Oxicams§	Meloxicam	q24h	7.5	15
	Piroxicam	q24h	20	40
Fenametes§	Meclofenamic acid+	q6-8h	150	400
	Mefenamic acid+	q6h	500 x 1, Then 250 q6h	1,000
Pyrazole§	Phenylbutazone	q6-8h	300	400

Protocol No.: FP01C-17-001

Second Step

SHORT/ACTING OPIOIDS For Moderate Pain				
Class	Generic Name	Dose (mg) II	Peak Effect, h	Duration, h
Morphine-like agonists	Codeine	32-65	1.5-2	3-6
	Dihydrocodeine	15-20	-	4-5
	Hydrocodone	-	0.5-1	4-6
	Meperidine (pethidine)	50	1-2	3-5
	Oxycodone	2.5	1	3-6
	Propoxyphene HCl	65-130	2-2.5	3-6
	Propoxyphene napsylate	100-200	2-2.5	3-6
Agonist-antagonist	Pentazocine	30	1.5-2	2-4
Other	Tramadol	-	2-3	4-6

Third Step

SHORT- AND LONG-ACTING OPIOIDS for Moderate to Severe Pain				
Class	Generic Name	Dose (mg)#	Peak Effect, h	Duration, h
Short Acting Morphine- like agonists	Morphine	10 IM	0.5-1	6
		20-60	1-2	4-7
		PO**		
	Hydromorphone	1.5 IM	0.5-1	4-5
		7.5 PO	1-2	4-5
	Meperidine (pethidine)	75 IM 300 PO	0.5-1 1-2	2-4 3-6

SHORT- AND LONG-ACTING OPIOIDS for Moderate to Severe Pain				
Class	Generic Name	Dose (mg)#	Peak Effect, h	Duration, h
	Oxycodone	20-30 PO	1-2	3-6
	Oxymorphone	1 IM 10 PR	0.5-1 1.5-3	3-6 4-6
Agents specifically indicated for breakthrough cancer pain in subjects with cancer	Oral transmucosal Fentanyl citrate (OTFC)	800 mcg PO	0.3-0.5	Related to blood levels of the drug
	Fentanyl buccal tablet	-	0.5-0.75	-
Partial agonist	Buprenorphine	0.4 IM	0.5-1	6-8
Mixed agonists-antagonists	Butorphanol	2 IM	0.5-1	3-4
	Nalbuphine	10 IM	0.5-1	3-6
	Pentazocine	60 IM 180 PO	0.5-1 1-2	3-6 3-6
Long-Acting				
Morphine-like agonists	Fentanyl transdermal system	25 mcg/h	24-72	72
	Levorphanol	2 IM 4 PO	0.5-1	6-8
	Methadone	10 IM 20 PO	0.5-1.5	4-8
	Modified-release morphine	20-30 PO**	3-4	8-24
	Modified-release	15-20	3-4	8-12

SHORT- AND LONG-ACTING OPIOIDS for Moderate to Severe Pain				
Class	Generic Name	Dose (mg)#	Peak Effect, h	Duration, h
	oxycodone	PO		
	Modified-release oxymorphone	10-15	3-4	12

ENDNOTES

* Consider using lower than recommended starting dose in the elderly, in subjects on multiple drugs, and in those with renal insufficiency (one half to two thirds recommended dose). Doses must be individualized. Low initial doses should be titrated upward if tolerated and clinical effect is inadequate. Doses can be increased in weekly increments. Studies of NSAIDs in the cancer population are meager; thus dosing guidelines are empiric.

+ Although clinical experience suggests that any of the NSAIDs may be analgesic, pain is an approved indication only for those drugs noted.

§ At relatively high doses, consider monitoring for adverse effects, e.g., by checking for occult fecal blood or for changes in liver function tests, blood urea nitrogen and creatinine assessments, or urinalysis.

II Oral dose that provides analgesia equivalent to 650 mg of aspirin. Starting dose may be higher or lower, and dose titration is needed after therapy is begun.

Dose that provides analgesia equivalent to 10 mg of IM morphine. The equianalgesic dose should not be interpreted as the starting, standard, or maximum dose, but rather as a guide; particularly useful in switching drugs or changing routes of administration. Depending on subject characteristics and prior opioid exposure, the starting dose can be lower or higher, and dose titration-either upward or downward-is repeatedly necessary in virtually all subjects.

** Extensive survey data suggest that the relative potency of IM to PO morphine of 1:6 changes to 1:2 or 1:3 with long-term dosing.

LITERATURE:

Russell K. Portenoy: Three-step analgesic ladder for management of cancer pain; Dept. of Pain Medicine and Palliative care, Beth Israel Medical Center, New York, New York