CLINICAL STUDY PROTOCOL

An Open-Label, Single-Arm Study of the Safety, Efficacy, and Pharmacokinetic Behavior of Leuprolide Mesylate for Injectable Suspension (LMIS 50 mg) in Subjects with Advanced Prostate Carcinoma – SAFETY EXTENSION

Protocol No.:	FP01C-13-001-EX
IND No.:	103206
Phase:	IIIb
Sites:	United States
Study Area:	United States
Study Drug:	Leuprolide Mesylate for Injectable Suspension (LMIS 50mg)
Version:	1.0
Date:	1-Oct-2015
Study Sponsor:	Foresee Pharmaceuticals Co., Ltd. 17F., NO3, Park St., NanKang Dist., Taipei 115, Taiwan, R.O.C. Contact: [redacted] Telephone number: [redacted]
CRO Information:	QPS, LLC 3 Innovation Way, Ste. 240 Newark, DE 19711
CRO Services:	Project management, Data Management (OpenClinica-eCRF), Medical Writing, Bio-Statistics, Safety, BA Lab
Medical Monitor:	[redacted] Contact number: [redacted]
Central Laboratory:	Physician's Reference Lab (PRL) 7800 W 110th St. Overland Park, KS 66210 1-913-338-4070 (US)

Compliance of Guidance and/or Rules and Regulations

This protocol is designed according to the International conference on harmonization (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).

CONFIDENTIAL

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 international conference on harmonization (ICH).

Affiliation	Name	Position	Signature	Date
Foresee Pharmaceuticals Co., Ltd.	[redacted]	Sponsor	[redacted]	Dec 4, 2015
QPS Holdings	[redacted]	Project Director	[redacted]	12/5/15
QPS Holdings	[redacted]	Medical Writer	[redacted]	12/3/15
QPS Holdings	[redacted]	Statistician	[redacted]	03Dec2015

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 Harmonization (ICH).

Name of investigator	Title	Signature	Date

Protocol Synopsis

Ⅰ. Protocol title:

An Open-Label, Single-Arm Study of the Safety, Efficacy, and Pharmacokinetic Behavior of Leuprolide Mesylate for Injectable Suspension (LMIS 50 mg) in Subjects with Advanced Prostate Carcinoma – SAFETY EXTENSION

Ⅱ. Objectives:

This is a Safety Extension study to Protocol FP01C-13-001. The primary objective of this study is to:

- Determine the safety and tolerability of LMIS 50 mg for up to 1 year under Protocol FP01C-13-001-EX (2 years of total exposure) in subjects with advanced prostate carcinoma;

Ⅲ. Study drug:

1. Name: Leuprolide Mesylate for Injectable Suspension(LMIS)
2. Dosage form: Prefilled and supplied in one sterile syringe, ready-to-use
3. Dose: 50mg (as the mesylate salt)
4. Active ingredient: Leuprolide mesylate
5. Dosing schedule: 50 mg leuprolide mesylate administered subcutaneously, when given as two separate injections 6 months apart (Month 12 and Month 18 from the initiation of Protocol FP01C-13-001).
6. Mechanism of action:
   The LH-RH agonist leuprolide, when given continuously, is known to inhibit pituitary gonadotropin secretion and suppress testicular and ovarian steroidogenesis. 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 concentrations in prostate cancer patients is a standard palliative treatment and slows cancer cell growth. LMIS 50 mg contains 50 mg leuprolide mesylate formulated in [redacted] and [redacted] to control and sustain the release of the bioactive leuprolide over a 6 month period after subcutaneous administration.
7. Pharmacological category: Antineoplastic agent, gonadotropin releasing hormone analog

Ⅳ. Developmental phase: phase ☐ Ⅰ ☐ Ⅱ ■ Ⅲb ☐ 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. 1 year (2 years total exposure)

6. Titration: □forced □optional ■none

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

Ⅵ. Endpoints

Primary endpoints:

1. Determine the safety and tolerability by:

- Clinically significant abnormal laboratory assessment (including liver function (AST, ALT, ALP), renal function (BUN, Serum Cr), complete blood count with platelets, clinical chemistries (K, Na, Mg, Ca and P), urinalysis, serum glucose, lipid profile (LDL, HDL, triglycerides) and HgbA1c)
- Adverse event (AE) reporting
- Clinically significant changes from baseline in 12-lead resting electrocardiograms (ECGs) per the Investigator's judgment

Ⅶ. Selection criteria:

1. Main inclusion criteria*:

(1) Complete 12 months of treatment with LMIS 50 mg under Protocol FP01C-13-001. If a subject wishes to enter the Extension study after more than 28 days following his end of study visit for Protocol FP01C-13-001, his serum testosterone level should be repeated at the screening visit to confirm that his castrate-level testosterone has been maintained.

(2) Laboratory values

- Absolute neutrophil count ≥ 1,500 cells/μL
- Platelets≥100,000 cells/μL
- Hemoglobin ≥ 10 gm/dL
- Total bilirubin ≤ 1.5 × upper limit of normal (ULN)
- AST (SGOT) ≤ 2.5 × ULN
- ALT (SGPT) ≤ 2.5 × 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

- HgbA1c within acceptable range according to investigator's opinion
- Clinical chemistries (K, Na, Mg, Ca and P) within acceptable range according to investigator's judgment
- Urinalysis within normal range according to the investigator's judgment

(3) Agree to use male contraceptive methods during study trial

(4) 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

(5) All aspects of the protocol explained and written informed consent obtained

*If the patient completed 12 months of treatment with LMIS 50 mg more than 28 days prior to entering the Extension study, the ECOG, PE, ECG, laboratory and PSA tests should be repeated.

If the patient has completed 12 months of treatment with LMIS 50 mg under Protocol FP01C-13-001 within the last 28 days, they will be allowed to enter the Extension study without repeating the testosterone measurements, ECG, PE, laboratory and the PSA tests.

2. Main exclusion criteria:

(1) Receipt of chemotherapy, immunotherapy, cryotherapy, radiotherapy, or anti-androgen therapy other than LMIS 50 mg under Protocol FP01C-13-001 for treatment of carcinoma of the prostate during the subject's participation in Protocol FP01C-13-001. Radiation for pain control will be allowed during the study.

(2) Receipt of any LHRH suppressive therapy within 6 months of Screening Visit OTHER THAN LMIS 50 mg under Protocol FP01C-13-001

(3) Subject has used prohibited treatments as listed in the Section 8.2 during participation in Protocol FP01C-13-001.

(4) Any pathological event, clinical adverse event, or any change in the subject's status at the end of FP01C-13-001 giving indication to the investigator that further participation in the study may not be the best interest of the subject

(5) Investigator considers that it is no longer feasible for the subject to be included in the extension study of LMIS 50 mg

(6) Subjects with persistent, non-castrate testosterone levels judged by the investigator

(7) 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) Screening failure

(2) Lost to follow-up

(3) Subject who decides to withdraw their informed consent

(4) Subject has used prohibited treatments as listed in the Section 8.2.

(5) Any pathological event, clinical adverse event, or any change in the subject's status giving indication to the investigator that further participation in the study may not be the best interest of the subject

(6) Investigator considers that it is no longer feasible for the subject to be included in the study

(7) Subjects with progression of prostate cancer, including but not limited to persistent, non-castrate testosterone levels judged by the investigator

Ⅷ. Study design:

This is a multi-center, open-label, single-arm safety extension study. All subjects will be males with advanced prostate carcinoma that have completed 12 months of therapy with LMIS 50 mg under Protocol FP01C-13-001, judged by investigators to be candidates for continued medical androgen ablation therapy, and all subjects will continue to receive LMIS 50 mg in an unblinded fashion.

All AE(s) and SAE(s) which occur during the study period will be recorded on the CRFs and followed until resolution, until the events are considered stable, or is otherwise explained. In addition, SAEs will be recorded and reported as required by both local and international regulatory requirements.

For early termination subjects, phone contacts should be performed at 3 and 6 months after the last injection of study drug 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 patient'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: This is a Safety Extension study to Protocol FP01C-13-001. No efficacy analysis will be conducted under this protocol. No sample size calculations have been conducted for this study.

3. Efficacy population: ☐ITT ☐PP ■other: NONE

(1) No efficacy analysis will be conducted in this study.

Safety population: ☐ITT ☐PP ■other:

(1) The Safety population will consist of any subject receiving a dose of LMIS 50 mg under Protocol FP01C-13-001-EX.

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

(1) No statistical analysis of efficacy will be conducted for this Safety Extension study

(2) Adverse events will be coded with MedDRA and a summary frequency table of adverse events will be provided. The severity and relationship to study medication of adverse events will be summarized as well. Furthermore, if any serious adverse events occur, the brief summary about serious adverse events will be described and listed in tables.

(3) The change of laboratory data, vital signs and 12-lead resting electrocardiograms (ECGs) will be summarized and assessed by paired t-test or Wilcoxon signed-rank test at a significance level of 0.05.

XI. Schedule of Assessments

	Scrn[1] (Subjects from FP01C-13-001 who completed study more than 28 days ago)	Scrn[2] (Subjects who completed the study within the last 28 days)	Treatment				ET[4]/EOS
Visit	1	1	2	3	4	5	6
Day (from completion of 12 months of treatment with LMIS 50 mg under FP01C-13-001)	-28-0	-28-0	0	84	168[3]	252	336
Informed consent	X	X					
Inclusion/Exclusion criteria	X	X					
Demographics	X	X					
Vital signs and height (as measured in Protocol FP01C-13-001) and weight[5](resting 3 minutes)	X	X	X	X	X	X	X
ECOG PS	X	X					
Physical Exam	X			X	X	X	X
12-Lead ECG (Supine 5 minutes)	X				X		X
Laboratory							
Hematology[6]	X			X	X	X	X
Biochemistry[7] (Fasting)	X			X	X	X	X
Urinalysis[8]	X			X	X	X	X
HgbA1c (Fasting)	X						X
PSA	X			X	X	X	X
Testosterone	X				X[9]		
Study treatment			X		X		
Concomitant treatments			X	X	X	X	X
Adverse events	X	X	X	X	X	X	X

Scrn: Screening; EOS: End of study; ET: Early termination; BP: Blood pressure; HR: Heart rate; RR: Respiratory rate; BT: Body temperature

1. If the patient completed 12 months of treatment with LMIS 50 mg more than 28 days prior to entering the Extension study, the testosterone level should be repeated and the repeat test should indicate that the patient maintains a castrate-level of testosterone. In addition, the ECOG, PE, ECG, laboratory and PSA tests should be repeated.

[2] If the patient has completed 12 months of treatment with LMIS 50 mg under Protocol FP01C-13-001 within the last 28 days, they will be allowed to enter the Extension study without repeating the testosterone measurements, ECG, PE, laboratory and the PSA tests.

[3] If the Day 168 (2nd injection, Visit 4) is delayed, have the subject return for subsequent visits according to the date when the first injection was received. DO NOT ADJUST THE TIMELINE DUE TO THE LATE INJECTION

[4] For early termination subjects (ET), procedures indicated should be performed. In addition, phone contacts should be performed at 3 and 6 months after the last injection of study drug to collect drug-related AEs, concomitant medication or non-drug therapy received for AEs treatment, disease progression status, and subject survival status.

[5] Vital signs include BP, HR, RR, and BT. Subject weight will be measured at Screening and EOS.

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

[7] 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)

[8] Urinalysis tests include pH, specific gravity, leukocyte, erythrocyte, protein.

[9] Testosterone Level test (Optional item depending on investigators' judgment)

Table of Contents

List of Abbreviations and Terms

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
AUA	American Urological Association
BDM	Biostatistics & Data Management
BLQ	Below Quantifiable Limit
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
F/U	Follow-up

GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GnRH	Gonadotropin-Releasing Hormone
Hb	Hemoglobin
Hct	Hematocrit
HDL	High Density Lipoprotein
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IP	Investigational Product
IRB	Institutional Review Board
IS	Internal Standard
ISC	Independent Statistical Center
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 for 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
PK	Pharmacokinetics
PLA	Poly (D, L-lactide)
PLG	Poly (D, L-lactide-coglycolide)
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
SC_r	Serum Creatinine
SOC	System Organ Class
SOP	Standard Operation Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Total Bilirubin
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

1. Introduction

1.1. Background Information

Prostate cancer is one of the leading causes of cancer deaths in men globally [1-2]. 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 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 the 1990s, 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 other medical conditions. In conjunction with radiation and chemotherapy, hormonal therapy is widely used in the treatment of advanced prostate cancer patients. Ample evidence has indicated 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. Various types of pharmaceutical agents have been developed to produce the effect of medical castration. Such agents include gonadotropin-releasing hormone (GnRH) agonist, GnRH antagonist, oestrogen agonist, and androgen inhibitors [6-8].

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 a 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 testosterone lowering GnRH agonist is considered the standard palliative therapy for prostate cancer patients. Leuprolide acetate was initially given by daily subcutaneous injections; recent improvement in depot formulations enabled convenient subcutaneous or intramuscular injection of leuprolide given on the monthly basis. A variety of sustained-release formulations are now being developed.

1.3. Study rationale

At the time of the initiation of this study, Foresee is conducting Protocol FP01C-13-001, entitled, “An Open-Label, Single-Arm Study of the Safety, Efficacy, and Pharmacokinetic Behavior of Leuprolide Mesylate for Injectable Suspension

(LMIS 50 mg) in Subjects with Advanced Prostate Carcinoma." In that protocol, it outlines that for subjects that complete 12 months of treatment with LMIS 50 mg and remain eligible for continued androgen deprivation therapy with LMIS 50 mg, the subject could receive up to 12 months of additional therapy with LMIS 50 mg. Protocol FP01C-13-001-EX represents the up to 12 months of additional therapy after completion of 12 months of treatment with LMIS 50 mg under Protocol FP01C-13-001.

It is important to note that subjects may be dosed under this protocol and followed for safety information up to the date of expiry of the clinical trial material (CTM) for this study. The date of expiry of the current CTM batch# CL0080 is May 31, 2016. Foresee expects to be able to extend the date of expiry to Nov 30, 2016 based on ongoing stability study. However, there is no guarantee that the expiry dating period can be successfully extended.

2. Study Objective and Endpoints

This is a safety extension of up to 12 months of additional treatment with LMIS 50 mg after the subject has completed 12 months of treatment under Protocol FP01C-13-001 and remain eligible for continued treatment with androgen deprivation therapy. Subjects participating in Protocol FP01C-13-001-EX will be followed for safety only.

2.1. Study Objective

Determine the safety and tolerability of LMIS 50 mg for up to 1 year under Protocol FP01C-13-001-EX (2 years of total exposure) in subjects with advanced prostate carcinoma.

2.2. Study Endpoints

1. Determine the safety and tolerability by:
    - Assessment of clinically significant abnormal lab data, including liver function (AST, ALT, ALP), renal function (BUN, Serum Cr), complete blood count with platelets, clinical chemistries (K, Na, Mg, Ca and P), urinalysis, serum glucose, lipid profile (LDL, HDL, triglycerides)and HgbA1c
    - Adverse event (AE) reporting
    - Clinically significant changes from baseline in 12-lead resting electrocardiograms (ECGs) per the Investigator's judgment

3. Study Design

3.1. Overall Design

This is a multi-center, open-label, single-arm safety extension study. All subjects will be males with advanced prostate carcinoma that have completed 12 months of therapy with LMIS 50 mg under Protocol FP01C-13-001, judged by investigators to be candidates for continued medical androgen ablation therapy, and all subjects will continue to receive LMIS 50 mg in an unblinded fashion.

All AE(s) and SAE(s) which occur during the study period will be recorded on the CRFs and followed until resolution, until the events are considered stable, or otherwise explained. In addition, SAEs will be recorded and reported as required by both local and international regulatory requirements.

For early termination subjects, phone contacts should be performed at 3 and 6 months after the last injection of study drug to collect drug-related AEs, concomitant medication or non-drug therapy received for AE treatment, disease progression status, and subject survival status.

4. Selection and Withdrawal of Subjects

4.1. Inclusion Criteria*

(1) Complete 12 months of treatment with LMIS 50 mg under Protocol FP01C-13-001. If a subject wishes to enter the Extension study after more than 28 days following his end of study visit for Protocol FP01C-13-001, his serum testosterone level should be repeated at the screening visit to confirm that his castrate-level testosterone has been maintained.

(2) Laboratory values

- Absolute neutrophil count ≥ 1,500 cells/μL
- Platelets≥100,000 cells/μL
- Hemoglobin ≥ 10 gm/dL
- Total bilirubin ≤ 1.5 × upper limit of normal (ULN)
- AST (SGOT) ≤ 2.5 × ULN
- ALT (SGPT) ≤ 2.5 × 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
- HgbA1c within acceptable range according to investigator's opinion
- Clinical chemistries (K, Na, Mg, Ca and P) within acceptable range according to investigator's judgment
- Urinalysis within normal range according to the investigator's judgment

(3) Agree to use male contraceptive methods during study trial

(4) 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

(5) All aspects of the protocol explained and written informed consent obtained

*If the patient completed 12 months of treatment with LMIS 50 mg more than 28 days prior to entering the Extension study, the ECOG, PE, ECG, laboratory and PSA tests should be repeated.

If the patient has completed 12 months of treatment with LMIS 50 mg under Protocol FP01C-13-001 within the last 28 days, they will be allowed to enter the Extension study without repeating the testosterone measurements, ECG, PE, laboratory and the PSA tests

4.2. Exclusion Criteria

(1) Receipt of chemotherapy, immunotherapy, cryotherapy, radiotherapy, or anti-androgen therapy other than LMIS 50 mg under Protocol FP01C-13-001 for treatment of carcinoma of the prostate during the subject's participation in Protocol FP01C-13-001. Radiation for pain control will be allowed during the study.

(2) Receipt of any LHRH suppressive therapy within 6 months of Screening Visit OTHER THAN LMIS 50 mg under Protocol FP01C-13-001

(3) Subject has used prohibited treatments as listed in the Section 8.2 during participation in Protocol FP01C-13-001.

(4) Any pathological event, clinical adverse event, or any change in the subject's status at the end of FP01C-13-001 giving indication to the investigator that further participation in the study may not be the best interest of the subject

(5) Investigator considers that it is no longer feasible for the subject to be included in a study of LMIS 50 mg

(6) Subjects with persistent, non-castrate testosterone levels judged by the investigator

(7) 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.

Study period:

Generally, subjects will be withdrawn from the study if any of the following occurs during the study period, i.e. from Screening Visit to end of study (EOS):

(1) Screening failure

(2) Lost to follow-up

(3) Subject who decides to withdraw their informed consent

(4) Subject has used prohibited treatments as listed in the Section 8.2.

(5) Any pathological event, clinical adverse event, or any change in the subject's

status giving indication to the investigator that further participation in the study may not be the best interest of the subject

(6) Investigator considers that it is no longer feasible for the subject to be included in the study

(7) Subjects with persistent, non-castrate testosterone levels judged by the investigator

Subjects who are withdrawn due to adverse event(s) or serious adverse event(s) should be followed until resolution or until the event is considered stable.

5. Study Treatment

5.1. Treatment plan summary

Subjects enrolled in this open-label, phase IIIb safety extension study will receive a single subcutaneous injection of LMIS 50mg every 6 months for up to 2 doses.

5.2. Treatment assignment

Subjects will be assigned the SAME SCREENING and RANDOMIZATION NUMBER(s) as was assigned to that individual subject under Protocol FP1C-13-001.

The randomization 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 carcinoma tend to accept this palliative treatment because its effects on gonadotropin are reversible when treatment is discontinued.

LMIS 50 mg is prefilled and supplied in a ready-to-use sterile syringe for subcutaneous injection. It contains 50 mg leuprolide mesylate [redacted] in a [redacted] formulation dissolved in a [redacted].

Investigational product dose administration procedures are outlined in the Investigational Product Instruction Manual.

5.4. Rationale for dose

The LMIS 50 mg dosage form has been developed to deliver bioactive leuprolide over a 6 month period after subcutaneous administration with a release profile similar to that of the Eligard® 45 mg formulation. The LMIS 50 mg dosage and its use as a sustained-release or depotdosage form have shown to be both efficacious and safe in similar leuprolide products (i.e. Eligard® 45 mg).

5.5. Warning and Precautions

Leuprolide acetate has the following established significant adverse events:

- 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 LHRH 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, anemia, and prolongation of the QT/QTc interval.

5.6. Packaging and labeling

LMIS 50 mg will be provided to the Investigator in a single use kit by Foresee Pharmaceuticals Co. Ltd. (previously as Foreseeacer Pharmaceuticals, Inc.), or its designee. The kit is packaged in a carton box and consists of a prefilled ready-to-use 1-mL sterile syringe, a sterile needle, and a silicone desiccant pouch to control moisture uptake. The prefilled syringes containing LMIS 50 mg (study drug) and the carton boxes in which the syringes are packaged both are labeled with a kit number. Each site will be provided with emergency back-up kits of study drug in case of contamination; the investigational sites will be directed to assign specific emergency kits to individual subjects by matching the subject's code to the kit label.

All study drug is minimally 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
- Expire date
- "Clinical trial use only"

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

It is important to note that subjects may be dosed under this protocol and followed for safety information up to the date of expiry of the clinical trial material (CTM) for this study. The date of expiry of the current CTM batch# CL0080 is May 31, 2016. Foresee expects to be able to extend the date of expiry to Nov 30, 2016 based on ongoing stability study. However, there is no guarantee that the expiry dating period can be successfully extended.

5.7. Supply, Delivery, Storage of Study Drug

LMIS 50mg is supplied by Foresee Pharmaceuticals Co. Ltd. (previously as Foreseeacer Pharmaceuticals, Inc.) The Investigational Product (IP) will be managed and stored safely and properly in a secured, lockable area by a designated, qualified person at the investigative site.

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.

The LMIS 50mg must be stored under refrigeration at 2 - 8℃.

5.8. Drug Dispensation and Accountability

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, expiration time/dates and the subject (randomization) 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 50mg via subcutaneous injection at the study site. The administration of the IP to the subject is under the supervision of the Investigator and controlled by the clinical site personnel delegated IP dispensing, preparation and administration roles by PI.

5.10. Treatment for Investigational Product Overdose

The single-dose LMIS 50 mg will be carefully administered to each subject in up to two doses 6 months apart by investigators or professional clinical site personnel officially delegated that responsibility by the investigator. If any accidental overdose injection is given, the subject should be closely monitored for safety until terminated from the study.

6. Study Procedures

This is a multi-center, open-label, single-arm safety extension study. After completing 12 months of treatment with LMIS 50 mg under Protocol FP01C-13-001 (with last dose under Protocol FP01C-13-001 approximately 6 months prior to Day 0 or Protocol FP01C-13-001-EX) and providing a written informed consent, subjects will be screened against baseline inclusion/exclusion criteria necessary for study eligibility. Eligible subjects will receive LMIS 50 mg from the prefilled syringes (without dilution or other mixing) in up to two single subcutaneous injections given 6 months apart.

After a single administration on Day 0, subjects will be evaluated, blood and urine samples collected, and other procedures performed as shown in the Table 1. The sign “X” indicates when the procedure should take place.

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/Early Termination) 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.

Table 1 **Schedule of Assessments**

	Scrn[1] (Subjects from FP01C-13-001 who completed study more than 28 days ago)	Scrn[2] (Subjects who completed the study within the last 28 days)	Treatment				ET[4]/EOS
Visit	1	1	2	3	4	5	6
Day (from completion of 12 months of treatment with LMIS 50 mg under FP01C-13-001)	-28-0	-28-0	0	84	168[3]	252	336
Informed consent	X	X					
Inclusion/Exclusion criteria	X	X					
Demographics	X	X					
Vital signs and height and weight[5](resting 3 minutes)	X	X	X	X	X	X	X
ECOG PS	X	X					
Physical Exam	X			X	X	X	X
12-Lead ECG (Supine 5 minutes)	X				X		X
Laboratory							
Hematology[6]	X			X	X	X	X
Biochemistry[7] (Fasting)	X			X	X	X	X
Urinalysis[8]	X			X	X	X	X
HgbA1c (Fasting)	X						X
PSA	X			X	X	X	X
Testosterone	X				X[9]		
Study treatment			X		X		
Concomitant treatments			X	X	X	X	X
Adverse events	X	X	X	X	X	X	X

Scm: Screening; EOS: End of study; ET: Early termination; BP: Blood pressure; HR: Heart rate; RR: Respiratory rate; BT: Body temperature

1. If the patient completed 12 months of treatment with LMIS 50 mg more than 28 days prior to entering the Extension study, the testosterone level should be repeated and the repeat test should indicate that the patient maintains a castrate-level of testosterone. In addition, the ECOG, PE, ECG, laboratory and PSA tests should be repeated.

[2] If the patient has completed 12 months of treatment with LMIS 50 mg under Protocol FP01C-13-001 within the last 28 days, they will be allowed to enter the Extension study without repeating the testosterone measurements, ECG, PE, laboratory and the PSA tests.

[3] If the Day 168 (2nd injection, Visit 4) is delayed, have the subject return for subsequent visits according to the date when the first injection was received. DO NOT ADJUST THE TIMELINE DUE TO THE LATE INJECTION

[4] For early termination subjects (ET), procedures indicated should be performed. In addition, phone contacts should be performed at 3 and 6 months after the last injection of study drug to collect drug-related AEs, concomitant medication or non-drug therapy received for AEs treatment, disease progression status, and subject survival status.

[5] Vital signs include BP, HR, RR, and BT. Subject weight will be measured at Screening and EOS.

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

[7] 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)

[8] Urinalysis tests include pH, specific gravity, leukocyte, erythrocyte, protein.

[9] Testosterone Level test (Optional item depending on investigators' judgment)

6.1. Screening Visit (Day -28 ~0 from End of Study Visit for FP01C-13-001)

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. 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 was signed. The following should be documented in the subject's medical chart: that they are participating in this study, document that informed consent has been obtained, and that a copy of the consent has been given to the subject.

(2) The Screening number for this study will be the Study Number used under Protocol FP01C-13-001

(3) Update the Medical History from what was collected under Protocol FP01C-13-001

(4) Update the medical/tumor history and medication from what was collected under Protocol FP01C-13-001

(5) Conduct a complete physical examination, including measurement of body weight (and body height as measured in Protocol FP01C-13-001). Measure and record the vital signs (after a 3 minute seated rest) including the measurement of blood pressure, heart rate, respiratory rate, and body temperature

(6) 12-Lead ECG (supine for at least 5 minutes)

(7) Record the ECOG PS

(8) Collect fasting 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
- HgbA1c

(9) Collect urine sample for urinalysis test

- pH, specific gravity, leukocyte, erythrocyte, protein

(10) Record any pre-treatment AE(s) NOTE: Open AEs from Protocol FP01C-13-001 will be recorded in this study file and noted in the database and other study documentation as, "AE under Protocol FP01C-13-001." These AEs should not be counted twice in the overall safety database.

*If the patient completed 12 months of treatment with LMIS 50 mg more than 28 days prior to entering the Extension study, the testosterone level should be repeated and the repeat test should indicate that the patient maintains a castrate-level of testosterone. In addition, the ECOG, PE, ECG, laboratory and PSA tests should be repeated.

If the patient has completed 12 months of treatment with LMIS 50 mg under Protocol FP01C-13-001 within the last 28 days, they will be allowed to enter the Extension study without repeating the testosterone measurements, ECG, PE, laboratory and the PSA tests.

6.2. Day 0 (approximately 6 months from last dose of LMIS 50 mg under Protocol FP01C-13-001)

Perform the following at 0 hr:

(1) Record subject enrollment number prior to dosing (same enrollment number as was used in FP01C-13-001 will be used in this study)

(2) Record vital signs prior to dosing

(3) Record concomitant medication(s) prior to dosing

(4) Record AE(s) prior to dosing and post dosing

(5) Administer LMIS 50 mg.

6.3. Day 84±7 days

(1) Conduct physical examination and record vital signs

(2) Collect fasting 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

(3) Collect urine sample for urinalysis test:

- pH, specific gravity, leukocyte, erythrocyte, protein

(4) Record concomitant medication(s)

(5) Record AE(s)

6.4. Day 168±7 days

(1) Conduct physical examination and record vital signs prior to dosing

(2) Collect fasting 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
- Testosterone Level (Optional item depending on investigators' judgment)

(3) Collect urine sample prior to dosing for urinalysis test:

- pH, specific gravity, leukocyte, erythrocyte, protein

(4) Conduct 12-Lead ECG

(5) Record concomitant medication(s) prior to dosing

(6) Record AE(s) prior to dosing and post dosing

(7) Administer LMIS 50 mg (second administration)

6.5. Day 252±7 days

(1) Conducted physical examinations and record vital signs

(2) Collect fasting 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

(3) Collect urine sample for urinalysis test:

- pH, specific gravity, leukocyte, erythrocyte, protein

(4) Record concomitant medication(s)

(5) Record AE(s)

6.6. Day 336±7 days (End of Study / Early Termination)

(1) Conduct physical examination and record vital signs

(2) Perform 12-lead ECG (5 minute supine)

(3) Collect fasting blood sample for analysis of:

- 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)
- HgbA1c
- PSA level

(4) Collect urine sample for urinalysis:

- pH, specific gravity, leukocyte, erythrocyte, protein

(5) Record concomitant medication(s)

(6) Record AE(s)

(7) Exit off the study

(8) For early termination subjects, phone contacts should be performed at 3 and 6 months after the last injection of study drug to collect drug-related AE, concomitant medication or non-drug therapy received for AE treatment, disease progression status, and subject survival status

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 adverse events. 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. 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 subjects collected under Protocol FP01C-13-001will be updated at the Screening Visit and used as the data for this study. The demographics will include date of birth, age, gender and ethnicity.

The general medical history and tumor history collected for participation in Protocol FP01C-13-001 will be used for this study.

7.1.3. Eligibility

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

7.2. Safety Assessment

7.2.1. Physical Examinations and Vital signs

Subjects will be examined at the Screening Visit, Day 84±7 days, Day 168±7 days, Day 252 ±7 days and Day 336±7 days 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 (Parts I and II).

Body weight will be measured. Body height in centimeters (cm) measured under Protocol FP01C-13-001 will be used for this study. Body weight will be measured at the Screening Visit and Day 336±7 days 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 (seated 3 minutes) blood pressures, heart rate, respiratory rate and body temperature.

*If the patient completed 12 months of treatment with LMIS 50 mg more than 28 days prior to entering the Extension study, the testosterone level should be repeated and the repeat test should indicate that the patient maintains a castrate-level of testosterone. In addition, the ECOG, PE, ECG, laboratory and PSA tests should be repeated.

If the patient has completed 12 months of treatment with LMIS 50 mg under Protocol FP01C-13-001 within the last 28 days, they will be allowed to enter the Extension study without repeating the testosterone measurements, ECG, PE, laboratory and the PSA tests.

7.2.2. Hematological / Biochemistry Examinations

Fasting blood samples will be collected for hematological, biochemistry and biological examinations.

Hematological tests will include complete blood count (CBC),including hemoglobin (Hb), hematocrit (Hct), red blood cells (RBC), white blood cells (WBC), WBC differential (neutrophils, eosinophils, basophils, lymphocytes and monocytes) platelet counts and HgbA1c. 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 HgbA1c, will be performed during the Screening Visit and at Day 84 ±7 days, Day 168±7 days, Day 252 ±7 days and Day 336±7 days. The HgbA1c will be performed at the final visit (Day 336 or End of Study Visit).

PSA will be performed at Day 84±7 days, Day 168±7 days (prior to dosing), Day 252±7 days, and at the final visit (Day 336±7 days or End of Study Visit).

The End of Study laboratory tests, HgbA1c and PSA assessments for Protocol FP01C-13-001 will be used as the Baseline assessment for this study.

Blood samples for laboratory tests will be collected in the hospital or at the investigative site and will be sent to the Central Laboratory for analyses.

*If the patient completed 12 months of treatment with LMIS 50 mg more than 28 days prior to entering the Extension study, the testosterone level should be repeated and the repeat test should indicate that the patient maintains a castrate-level of testosterone. In addition, the ECOG, PE, ECG, laboratory and PSA tests should be repeated.

If the patient has completed 12 months of treatment with LMIS 50 mg under Protocol FP01C-13-001 within the last 28 days, they will be allowed to enter the Extension study without repeating the testosterone measurements, ECG, PE, laboratory and the PSA tests.

7.2.3. Urinalysis

A urine sample will be collected for urinalysis. The urinalyses will include urine pH, specific gravity, leukocyte, erythrocyte and protein.

The urinalysis will be performed at Screening, Day 84 ±7 days, Day 168±7 days (prior to dosing), Day 252 ±7 days and Day 336±7 days (or End of Study Visit).

The End of Study urinalysis for Protocol FP01C-13-001 will be used as the Baseline

assessment for this study.

Urine samples will be collected in the hospital or at the investigative site and will be sent to the Central Laboratory for analyses.

*If the patient completed 12 months of treatment with LMIS 50 mg more than 28 days prior to entering the Extension study, the testosterone level should be repeated and the repeat test should indicate that the patient maintains a castrate-level of testosterone. In addition, the ECOG, PE, ECG, laboratory and PSA tests should be repeated.

If the patient has completed 12 months of treatment with LMIS 50 mg under Protocol FP01C-13-001 within the last 28 days, they will be allowed to enter the Extension study without repeating the testosterone measurements, ECG, PE, laboratory and the PSA tests.

7.2.4. ECG

An ECG will be performed by standard 12-lead at the Screening Visit for eligibility and on Day 168±7 days prior to dosing and on Day 336±7 days (or End of Study Visit).

*If the patient completed 12 months of treatment with LMIS 50 mg more than 28 days prior to entering the Extension study, the testosterone level should be repeated and the repeat test should indicate that the patient maintains a castrate-level of testosterone. In addition, the ECOG, PE, ECG, laboratory and PSA tests should be repeated.

If the patient has completed 12 months of treatment with LMIS 50 mg under Protocol FP01C-13-001 within the last 28 days, they will be allowed to enter the Extension study without repeating the testosterone measurements, ECG, PE, laboratory and the PSA tests.

7.2.5 Adverse Events

Subjects will be asked to report adverse events voluntarily. The investigator will also question and examine the subjects to identify any adverse events at each visit (including Screening Visit). See **Section 9 Adverse Events (AE)** and **Serious Adverse Events (SAE)** for detailed information on adverse events.

8. Concomitant treatment

All concomitant medications, both permitted and prescribed, 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.

The treatments recorded prior to and during participation in Protocol FP01C-13-001-EX will be recorded. Moreover, all concomitant medications administered for the treatment of an adverse event 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 patient'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 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 on 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, 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 >10mg/d

Subjects who have received these prohibited treatments should be withdrawn from the trial.

8.3. Rescue medication and treatment

If the event of an emergency, the investigator will institute clinical life-support procedures according to the individual situation.

9. Safety Monitoring

9.1. Adverse events (AEs)

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 adverse events if they are not clinically significant. They will only be recorded as adverse events if a therapeutic action is needed or the investigator judges them to be clinically significant.

The occurrence of adverse events should be sought by non-directive questioning of the subject at each visit and/or telephone follow-up during the study. Adverse events 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 adverse events 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 a serious adverse event (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 described in Table 9-1.

Table 9-1 Intensity scales of AE

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.

Activities of Daily Living (ADL):

*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 9-2.

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

Table 9-2 The relationship between AE and study drug

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 (SAEs)

An SAE is any experience that suggests a signification 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.
- The medical monitor for this study is :

  [redacted]

  Contact number: [redacted]

  Email: [redacted]

9.3. Serious adverse events reporting requirement and emergency procedures

Whether or not related to the study medication, any adverse event which is fatal or life threatening that occurs during the study must be reported promptly (within 24 hours) to the sponsor (Foresee) or QPS. 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 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/ECs 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

This a Safety Extension Study to Protocol FP01C-13-001. No efficacy analysis will be conducted under this protocol. No sample size calculations have been conducted for this study.

10.2. Analysis population

The Safety population will be used in the safety assessment for this study. The Safety population will consist of any subject receiving at least one dose of LMIS 50 mg under protocol FP01C-13-001-EX

10.3. Safety analysis

The transition matrix will be summarized for the following:

- Change from baseline in vital signs (BP, HR, RR)
- Change from baseline in physical examinations (including weight)

The summary results of vital signs (BP, HR, RR) and weight at Baseline, End of Study Visit, and the change from baseline will be summarized descriptively. Also the change from baseline to the End of Study Visit 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 will be summarized.

- Change in laboratory data, including liver function (AST, ALT, ALP), renal function (BUN, Serum Cr), complete blood count with platelets, clinical chemistries (K, Na, Mg, Ca and P), urinalysis, serum glucose, and lipid profile (LDL, HDL, triglycerides) and HgbA1c

The summary results of laboratory data at the Baseline and the End of Study Visit, and change from baseline to End of Study Visit will be summarized by descriptive statistics and paired t-test or Wilcoxon signed- rank test will be used at a significance level of 0.05.

- Adverse event (AE) reporting

The analysis of adverse events 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. Adverse event incidence rates will be analyzed by severity and relationship to study drug. Any adverse event leading to death, discontinuation from the study, or change of dose will be listed as per regulation.

If any serious adverse event occurs, a brief summary about the serious adverse event will be described and listed.

- Change in 12-lead resting electrocardiograms (ECGs)

The summary results of 12-lead resting ECG at Baseline and the End of Study Visit will be summarized descriptively. The transition matrix for ECGs will be summarized.

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. For the US sites those regulatory documents are considered primary.

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 serious adverse events, as defined in the protocol, to the IRB/EC 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 (or the subject's legal representative, if appropriate) 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 Harmonization (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 5th revision (2000). 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 investigative site should retain the records of the trial subjects forever. 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.

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 (or their legal representatives) must also agree to allow access to the subjects' medical records, and they will be informed of this and will be signing their agreement when giving informed consent. 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 and GCP 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. 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.

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 developed withdrawal criteria 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.

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. Examples include subject noncompliance with medication, surreptitious use of medications prohibited by the protocol, inability or unwillingness to accurately report adverse events or concomitant medication use.

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 the end of the follow-up visit or at the Early Termination Visit.

19. Termination of Study

Foresee Pharmaceuticals Co., Ltd. and QPS reserve the right to discontinue this trial at any time.

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.

22. References

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23. Appendix I

Pain in cancer patients 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-13-001-EX 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:

1_{ST} STEP

NONOPIOID ANALGESICS for Mild to Moderate Pain

Class	Generic Name	Dosing Schedule	Recomended Starting Dose mg/d*	Maximum
p-Aminophenol derivative	Acetaminophen+ (paracetamol)	q4-6h	2,600	4,000
COX-2- selective inhibitors	Celecoxib+	q12h	200	600
Salicylates §	Aspirin+	q4-6h	2,600	6,000
	Choline magnesium trisalicylate+	q12h	1,500 x 1, then 1,000 q12h	4,000
	Diflunisal+	q12h	1,000 x 1, then	1,500

			500 q12h	
	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
	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

2_{ND} 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

3rd 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 20-60 PO**	0.5-1 1-2	6 4-7
	Hydromorphone	1.5 IM 7.5 PO	0.5-1 1-2	4-5 4-5
	Meperidine (pethidine)	75 IM 300 PO	0.5-1 1-2	2-4 3-6
	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 patients 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 oxycodone	15-20 PO	3-4	8-12
	Modified-release oxymorphone	10-15	3-4	12

ENDNOTES

* Consider using lower than recommended starting dose in the elderly, in patients 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, eg, by checking for occult fecal blood of for changes in liver function tests, blood urea nitrogen and creatinine

assessments, or urinalysis.

ll 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 10mg 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 patient characteristics and prior opioid exposure, the starting dose can be lower of higher, and dose titration-either upward or downward-is repeatedly necessary in virtually all patients.

****** 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