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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Camcevi

International non-proprietary name: leuprorelin

Procedure No. EMEA/H/C/005034/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADPC	The analysis dataset containing the PK concentrations
ADR	Adverse drug reaction
ADT	Androgen deprivation therapy
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ASMF	Active substance master file
AST	Aspartate aminotransferase
AUA	American Urological Association
AUC	Area under concentration curve
BET	Bacterial endotoxin test
BfArM	German federal institute for drugs and medicinal devices
BUN	Blood urea nitrogen
CMA	Critical material attribute
Cmax	Maximum concentration
Cmin	Minimum concentration
CPP	Critical process parameter
CQA	Critical quality attribute
Css	Concentration at steady state
CV%	Coefficient of variation
DoE	Design of experiments
DRE	Digital rectal examination
e.g.	For example (*Exempli gratia*)
ECG	Electrocardiogram
ECOG	Eastern co-operative oncology group
EMA	European medicines agency
EOS	End of study
FAERS	FDA adverse event reporting system
FDA	Food and drug administration (of USA)
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GnRH	Gonadotropin releasing hormone
GPC	Gel permeation chromatography
HCP	Health care professional
HDL	High-density lipoprotein
HF	Human factor
HgbA1c	Glycosylated haemoglobin
i.e.	that is (*id est*)
ICH	International congress of harmonisation
IDMC	Independent data monitoring committee
IFU	Instructions for use
ISC	Independent statistical centre
ITT	Intent to treat
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LDL	Low-density lipoprotein

LH	Luteinizing hormone
LH-RH	Luteinizing hormone releasing hormone
LLOQ	Low limit of quantitation
LMIS	Leuprorelin mesilate injectable suspension
MAA	Marketing authorisation application
MAR	Missing at random
max	Maximum
MDD	Medical device directive
MeDRA	Medical dictionary for regulatory activities
min	Minimum
Mw	Molecular weight by weight
Mn	Molecular weight by number
n	Number or sample size
NMT	No more than
NOAEL	No observed adverse events level
NPM	N-methylpyrrolidone
OOS	Out of specification
OTC	Over the counter (medications)
PD	Pharmacodynamic(s)
PFS	Pre-filled syringe
PIP	Paediatric investigation plan
PK	Pharmacokinetic(s)
PLA	Poly(D,L-lactide)
PLG	Poly(D,L-lactide-co-glycolide)
PP	Per protocol
PSA	Prostate specific antigen
PT	Preferred term
QbD	Quality by design
QC	Quality control
QD	Once daily (*Quaque die*)
QTPP	Quality target product profile
RBC	Red blood cell count
RMP	Reference medicinal product or Risk management plan
SA	Scientific advice
SAE	Serious adverse event
SC	Subcutaneous(ly)
SCS	Summary of clinical safety
SD	Standard deviation
SE	Standard error
TEAE	Treatment emergent adverse event
TFA	Trifluoroacetic acid
Tmax	Time to maximum concentration
ULN	Upper limit of normal
URRA	Use-related risk analysis
VAS	Visual analogue scale
WBC	White blood cell count

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 6 March 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Camcevi, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 April 2018. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The applicant applied for the following indication

CAMCEVI is indicated for the treatment of hormone dependent advanced prostate cancer and for the treatment of high-risk localised and locally advanced hormone dependent prostate cancer in combination with radiotherapy

The legal basis for this application refers to:

Article 10(3) of Directive 2001/83/EC as amended- hybrid application.

The application submitted is composed of administrative information, complete quality data, an indirect comparison of own clinical data with the clinical data of the reference medicinal product Eligard and with appropriate own applicant's non-clinical data.

1.2. Information on paediatric requirements

Not applicable. A class waiver (for sex hormones) and exemption from Regulation (EC) No 1901/2006 requirements (due to Application type).

1.3. Information relating to orphan market exclusivity

1.3.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.5. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johanna Lähteenvuo Co-Rapporteur: Bruno Sepodes

For the appointed CHMP rapporteur it was considered exceptionally justified that the individual had previously been acting as coordinator for Scientific advice on the development relevant for the indication subject to the present application. The justification was as follows:

The appointed CHMP co-rapporteur had no such prominent role in Scientific advice relevant for the indication subject to the present application.

The application was received by the EMA on	6 March 2020
The procedure started on	26 March 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 June 2020
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	22 June 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 June 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 July 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 November 2020
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	08 December 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 January 2021
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	27 January 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 February 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	09 March 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Camcevi on	24 March 2022

2. Scientific discussion

2.1. Problem statement

The applicant applies for the same therapeutic use of those approved for the reference product Eligard 45.

Camcevi is indicated for the treatment of hormone dependent advanced prostate cancer and for the treatment of high-risk localised and locally advanced hormone dependent prostate cancer in combination with radiotherapy.

2.1.1. Disease or condition

Prostate cancer is one of the leading causes of deaths in men globally. 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.

Population-based screening of men aged between 55 and 69 years, using prostate-specific antigen (PSA) testing, has been evaluated in randomised trials. After a median follow-up of 13 years, the European screening trial demonstrated a relative reduction in the risk of prostate cancer mortality of 21% (29% if adjusted for non-compliance). However, 781 men needed to be invited for screening and 27 patients needed to be treated to prevent one death from prostate cancer. Risk-adapted early detection of prostate cancer using a baseline PSA level has also been evaluated in retrospective cohort studies. The baseline PSA at or before the age of 50 years is associated with the risk of prostate cancer mortality over the subsequent 25 years. The risk of clinically significant prostate cancer is related to age, ethnicity, family history, PSA level, free/total PSA ratio and findings on digital rectal examination (DRE) (ESMO Clinical Practice Guideline, Parker et al. 20151).

2.1.2. Epidemiology

Worldwide, prostate cancer ranks second in cancer incidence and fifth in cancer mortality in men (Bray et al, 2018). In Europe, the estimated number of new prostate cancer cases was approximately 473,344 in 2020 and the number of deaths was approximately 108,088 in 2020 (GLOBOCAN, 2020).

2.1.3. Biologic features, aetiology and pathogenesis

The aetiology and pathogenesis of prostate cancer remain still unclear. Several factors have been identified to predispose for the development of prostate cancer including genetic predisposition, diet, infection, hormonal imbalance and toxins. In this context, it is not surprising that the incidence is increasing, particularly in Western countries. The majority of the cancers in the prostate are adenocarcinomas, which can be divided to subtypes based on histological and molecular features. Despite the heterogeneity seen in all cancer types, the role of androgens connects all the subtypes from localised to advanced prostate cancer. Thus, antiandrogen treatment (ADT) by surgical or chemical castration is the mainstay of treatment. The natural course of prostate cancer is the development from hormone-sensitive to hormone-refractory prostate cancer (i.e., castration-resistant prostate cancer)[2].

Clinical presentation, diagnosis and stage/prognosis

High-grade prostate cancer can occur in men with a 'normal' PSA level. After a previous negative biopsy, indications for repeated biopsies include a rising PSA, suspicious digital rectal examination (DRE), abnormal multi-parametric magnetic resonance imaging (MRI), atypical small acinar

[1] Parker C. et al. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2015:26;v89-v77. Doi:10.1093/annonc/mdv222.
[2] Henrik Grönberg, 2003

proliferation or multifocal high-grade prostatic intraepithelial neoplasia. The most important prognostic factors are the stage, differentiation, and PSA level at diagnosis[1].

Localised disease should be classified as low-risk (T1-T2a and Gleason score (GS) ≤6 and PSA ≤10), intermediate-risk (T2b and/or GS7 and/or PSA 10-20) or high-risk (≥T2c or GS8-10 or PSA >20) as a guide to prognosis and therapy. The risk classification is based on TNM staging, Gleason score and PSA level. Gleason score is based upon the microscopic appearance ranging from 1 to 5 [3].

Clinical T stage should be evaluated by DRE. MRI provides more accurate T staging and can inform surgical technique, both with respect to nerve sparing and wide excision of areas of potential extra-prostatic extension. Within the low-risk category, higher % positive cores, length of core involvement, PSA density and a lower f/t PSA ratio are associated with the risk of under-staging. Patients with intermediate- or high-risk disease should have nodal staging using computed tomography (CT), MRI, choline positron emission tomography/CT (PET/CT) or pelvic nodal dissection. Patients with intermediate- or high-risk disease should be staged for metastases. General health and co-morbidities should be assessed. Patients who are not suitable for treatment with curative intent, by virtue of poor general health, do not normally require staging investigations (ESMO Clinical Practice Guideline, Parker *et al*. 2015[1]).

2.1.4. Management

Therapeutic choice for the treatment of prostate cancer is determined based on age, tumour grade and stage as well as other medical conditions. There is no consensus regarding optimum management of localised disease. Patients should be informed of the potential benefits and harms of the different options. In localised disease, patients can be treated with radiotherapy, surgery or active surveillance. In conjunction with radiation and chemotherapy, hormonal therapy is widely used in the treatment of prostate cancer patients (Parker et al., 20151). Evidence suggests 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 (Sasse et al., 20124; Tamburrino et al., 20125).

On this basis, the ADT has been the mainstay of hormonal treatment for prostate cancer over the years. Various types of pharmaceutical agents have been developed for medical androgen deprivation, including GnRH agonists, GnRH antagonists, oestrogen agonists, anti-androgens and androgen pathway inhibitors and androgen inhibitors (Hoda et al., 20176).

The leuprorelin-based hormonal ADT is the mainstay of treatment for locally advanced and metastatic prostate cancer, as well as for the adjuvant treatment of patients with intermediate-risk or high-risk localised prostate cancer. Leuprorelin ADT has been shown to improve quality of life and prolong life in prostate carcinoma patients (Hoda *et al*., 2017[5]; Sethi and Sanfilippo, 2009[7]).

Clinical pharmacological properties and efficacy and safety of leuprorelin in ADT in neoadjuvant or palliative prostate cancer treatment have been well characterised (Hoda *et al.*, 2017[5]; Sethi and Sanfilippo, 2009[6]), and leuprorelin clinical practice experience comprises about three decades, with the

[3] Rao et al. Validation of the WHO 2016 new Gleason score of prostatic carcinoma. Urol Ann 2018;10:324-9.
[4] Sasse AD, Sasse E, Carvalho AM and Macedo LT (2012). Androgenic suppression combined with radiotherapy for the treatment of prostate adenocarcinoma: a systematic review. BMC Cancer 2012, 12:54.

[5] Tamburrino L, Salvianti F, Marchiani S, Pinzani P, Nesi G, Serni S, Forti G, Baldi E, Androgen receptor (AR) expression in prostate cancer and progression of the tumor: Lessons from cell lines, animal models and human specimens. Steroids 2012; 77(10): 996-1001.
[6] Hoda MR, Kramer MW, Merseburger AS, Cronauer MV. Androgen deprivation therapy with Leuprolide acetate for treatment of advanced prostate cancer. Expert Opin Pharmacother. 2017 Jan;18(1):105-113.
[7] Sethi R, Sanfilippo, N. Six-month depot formulation of leuprorelin acetate in the treatment of prostate cancer. Clin Interv Aging 2009;4:259-267.

first leuprorelin 1-mg products required to be injected at a daily basis, followed by more convenient leuprorelin depot forms during the last 20 years.

2.2. About the product

This is a marketing authorisation application (MAA) for a leuprorelin mesilate injectable suspension (LMIS) 50 mg, containing leuprorelin mesilate equivalent to 42 mg leuprorelin (Camcevi 42 mg), supplied as ready-to-use drug product in contrast to the available products requiring pre-mixing prior subcutaneous injection. The LMIS 50 mg is proposed for the treatment of hormone-dependent advanced prostate cancer and for the treatment of high-risk localised and locally advanced hormone dependent prostate cancer in combination with radiotherapy. LMIS 50 mg is foreseen for a single subcutaneous injection every six months, likewise other approved leuprorelin-containing depot formulations of comparable leuprorelin strength (*e.g.*, the reference product Eligard 45 mg).

Leuprorelin is a gonadotropin releasing hormone (GnRH) agonist. Leuprorelin is a synthetic nonapeptide analogue of naturally occurring GnRH that, when given continuously at therapeutic doses, inhibits pituitary gonadotropin secretion and suppresses testicular and ovarian steroidogenesis. The analog possesses greater potency than the natural hormone. Initial administration of leuprorelin causes an increase in gonadotropin levels (LH, FSH), which can last for several weeks, leading to a transient rise in gonadal steroid production during that time (testosterone and dihydrotestosterone in males, and oestrone and estradiol in pre-menopausal females). For this reason, the concomitant use of an anti-androgen is recommended in male patients as anti-androgen flare protection. With continuous administration, there is eventual suppression of gonadotropin release within 2 to 4 weeks. In males, testosterone is reduced to castrate levels (below the castrate threshold or ≤ 50 ng/dL). Upon removal of the drug, this effect is reversible. The biological effect of the GnRH agonist leuprorelin is time- and not concentration-dependent, and PK profiles among different leuprorelin forms may vary as long as serum leuprorelin levels are maintained within an established therapeutic range (0.2 to 2.0 ng/mL) to produce affective serum testosterone suppression.

LMIS 50 mg differs from currently approved leuprorelin products in the salt used for the proposed drug product, mesilate instead of acetate. LMIS 50 mg is a pre-mixed product containing leuprorelin mesilate equivalent to 42 mg leuprorelin, which is formulated in a solution of N-methylpyrrolidone (NMP) and poly (D,L-lactide, PLA). The difference in salt weight has been accounted for so that the free base equivalent is the same between the proposed LMIS 50 mg product and the currently approved 45 mg leuprorelin acetate products.

The LMIS 50 mg delivery system resembles the gel-based delivery system (Atrigel) used for a marketed product Eligard depot formulations globally. The gel based leuprorelin formulations deliver the drug by using a biodegradable polymer of D,L-lactide-co-glycolide dissolved in N-methylpyrrolidone. The Atrigel delivery system was developed to improve the pharmacokinetic (PK) profile leading to reliable and sustained testosterone suppression. However, in contrast to currently approved depot / prolonged-release leuprorelin products, which require reconstitution prior to use, LMIS 50 mg will be supplied as ready-to-use drug product (no premixing will be required prior to SC injection), pre-filled in a single, sterile syringe.

The MAA for LMIS 50 mg was submitted under Article 10(3) of Directive 2001/83/EC using Eligard 45 mg as a reference product and is intended to be used in the same indications as the reference product.

2.3. The development programme/compliance with CHMP guidance/scientific advice

No Scientific Advice from CHMP was given for this procedure.

In the EU, only national scientific advice was sought at the German Federal Institute for Drugs and Medical Devices (BfArM) in January 2017. This Scientific Advice (SA) was particularly on non-clinical and clinical development and the bridging concept to Eligard 45 mg. The hybrid application under Article 10(3) of Directive 2001/83/EC with the reference product Eligard and the clinical development study design were considered acceptable provided that the bridging can be shown. Regarding the proposed safety data, the final safety data generated from the pivotal Phase 3 trial was considered essential with special emphasis on local or administration site adverse events and reactions (Refer to Section Clinical safety). Other questions concerned toxico-pharmacological development and chemical, pharmaceutical and biological development. The applicant followed this national SA considerably well taking into consideration that the advice was rather straightforward leaving the scientific bridging to be constructed by the applicant.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as prolonged-release suspension for injection containing 42 mg of leuprorelin. The product contains the mesilate salt.

Other ingredients are: poly(D,L-lactide) and N-methylpyrrolidone.

The product is available in cyclic olefin copolymer pre-filled syringe closed with bromobutyl elastomeric grey tip cap, plunger and finger grip as described in section 6.5 of the SmPC.

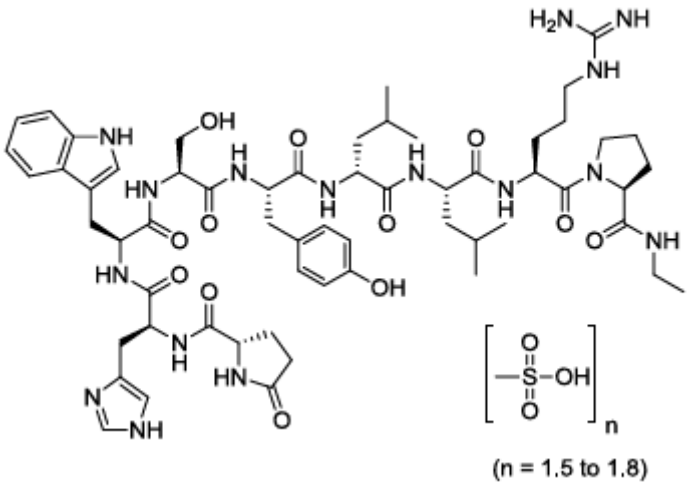
Camcevi contains a blister with a sterile pre-filled syringe, a sterile needle and a Point-Lok needle protection device (non-sterile).

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of leuprorelin is 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-Dleucyl-L-leucyl-L-arginyl-*N*-ethyl-L-prolinamide mesilate corresponding to the molecular formula $C_{59}H_{84}N_{16}O_{12} \bullet (CH_4O_3S)_n$, n = 1.5 – 1.8. It has a molecular weight of 1209.41 g/mol (free base) and the following structure:

Figure 1. Active substance structure



The chemical structure of leuprorelin was elucidated by a combination of elemental analysis, ultraviolet spectroscopy, mass spectrometry, Fourier transform infrared, nuclear magnetic resonance and circular dichroism. The solid state properties of the active substance were measured by X-ray powder diffraction.

The active substance is a white to off-white hygroscopic powder. It is a freely soluble substance across physiological pH ranges. Leuprorelin mesilate is a stable salt form of leuprorelin.

Leuprorelin exhibits stereoisomerism due to the presence of nine chiral centres. The provided characterisation data in section confirm that the active substance manufacturing process produces a single enantiomer of desired enantiomeric purity. Enantiomeric purity is controlled routinely by chiral UPLC and specific optical rotation.

Polymorphism has not been observed for leuprorelin.

2.4.2.2. Manufacture, characterisation and process controls

The active substance is synthesised by solid phase peptide synthesis using commercially available protected amino acids as building blocks. Quality of amino acids is controlled by suitable specifications.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory. A single ASMF is used to support this Marketing Authorisation Application.

The active substance manufacturing process consists of the following main process steps: solid-phase peptide synthesis, cleavage of the peptide from the resin and deprotection, amidation, trifluoroacetic acid (TFA) salt formation, purification, salt-exchange, evaporation and lyophilisation.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are considered acceptable.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities, including potential genotoxic impurities, were well discussed with regards to their origin and characterised.

The primary packaging of the active substance complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

2.4.2.3. Specification

The active substance specification includes tests for: appearance, identification (mass spectrometry, UPLC), solubility (in house), amino acid analysis (in house), assay (UPLC), purity (UPLC), alkyl methanesulfonates (GC), acid content (IC), residual solvents (HS-GC), water content (KF), specific rotation (Ph. Eur.), residue on ignition (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and microbiological examination (Ph. Eur.).

The specification of leuprorelin mesilate follows the principles of Ph. Eur. monograph of leuprorelin and USP monograph of leuprolide acetate. Total impurities and bacterial endotoxins have tighter limits than compendial leuprorelin. As the substance is a mesilate salt, limits have been set for acid content, ratio of methanesulfonic acid to peptide, and alkyl methanesulfonates as per ICH M7 guidance.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on three commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (-20 ± 5ºC) and for up to 6 months under accelerated conditions (5 ± 3ºC) according to the ICH guidelines were provided.

The samples were tested for all stability indicating parameters included in the specification. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications.

Photostability testing following the ICH guideline Q1B was performed on one batch. The results show that the active substance is sensitive to light under direct exposure while the sample packed in the proposed container closure system is resistant to the photolytic effect.

Forced degradation studies were performed to evaluate the suitability of the analytical methods as stability indicating. The peptide was exposed to acid, base, oxidation and thermal conditions. The results show that analytical methods used for assay and purity testing are stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period under recommended storage conditions in the proposed container.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Camcevi is presented as a sterile prolonged-release suspension for subcutaneous injection. It is an off-white to pale yellow viscous and opalescent product, free from visible particles and foreign matter with

potential air bubbles, contained in a 1 ml long-barrel, colourless to pale yellow plastic pre-filled syringe closed with a grey elastomeric tip cap and a plunger. The sterilised, pre-filled and capped syringe is co-packed with a sterile, capped needle and placed in secondary packaging consisting of a thermoformed blister. The blister is placed together with a non-sterile Point-Lok needle protection device and package leaflet in a cardboard carton. The hypodermic needle is classified into Class IIa according to the Medical Device Directive (MDD 93/42/EEC) and is CE-marked. A valid Declaration of Conformity has been presented.

The aim of the pharmaceutical development was to result in a product similar to the reference product Eligard 45 mg powder and solvent for solution for injection, and to have enhanced stability to allow the product to be pre-filled into a single, ready-to use syringe for easier administration. The development included the device constituents (i.e., sterile pre-fillable syringe and sterile, capped, hypodermic thin-wall needle) in establishing design requirements for Camcevi.

The applicant has applied quality by design (QbD) principles in the development of the finished product and their manufacturing process. However, no design spaces have been claimed for the manufacturing process of the finished product. Risk assessments have been used throughout the QbD approach to identify potential critical material attributes (CMAs) and critical process parameters (CPPs), and to determine which studies are necessary to achieve product and process understanding.

Three excipients are used in the finished product formulation of Camcevi. The compendial excipients are N-methylpyrrolidone (NMP) and nitrogen. The non-compendial excipient is poly(D,L-lactide) (PLA).

None of the excipients are of human or animal origin or is a novel excipient; *e.g.*, PLA is present in Leuprorelin Hexal, DE/H/1681/0002 and NMP is present in Eligard, DE/H/058/003.

Satisfactory description of the analytical procedures and validation data have been provided for the non-compendial excipient, PLA. The specifications have been properly justified based on development studies and applicable guidance and compendial methods.

The excipient functions, their CMAs, as well as their compatibility with the active substance have been sufficiently discussed. NMP is Class 2 solvent with a PDE of 5.3 mg/day (ICH Q3C) but, it is used also in other medicinal products authorised in the EU with similar or higher concentration, and the applicant has adequately justified the use of NMP in Camcevi (see also non-clinical part of this assessment report).

The impact of the CMAs on Camcevi CQAs has been evaluated using prior knowledge or by conducting specific studies.

The risk assessment results as well as the control strategy for the components are endorsed as all CMAs that could affect the finished product CQAs are controlled in the raw material specifications.

A non-compendial method has been developed for accelerated *in vitro* release for quality control purposes only, as *in vitro-in vivo* correlation cannot be established for Camcevi. Acceptable specification limits have been established based on the results obtained for the batches used in the clinical trials. Furthermore, discriminatory nature of the method has been adequately demonstrated.

The manufacturing process consists of the following main steps: weighing, compounding, filtration, degassing, filling, and terminal sterilisation by gamma irradiation. The sterilisation is performed with a minimum absorbed dose of 25 kGy, which is considered as a standard acceptable sterilisation dose according to the Ph. Eur. Possible impact of the sterilisation process on the finished product has been sufficiently investigated.

The manufacturing process development has been extensively described and actual CPPs have been identified through a second design of experiments (DoE) study, in which sensitivity of the finished

product CQAs to deliberate changes of the potential CPP levels was investigated. This study has been performed by the finished product manufacturer using industrial equipment intended to be used for Camcevi commercial batches.

The functional relationships and process understanding obtained during development have been utilised in establishing a control strategy, which consists of control of material attributes, control of the critical process parameters, IPCs, and release and stability testing of the finished product. Based on the specifications established for all components and the finished product, and the process validation performed with three consecutive production scale batches, the proposed control strategy is endorsed.

The primary packaging is cyclic olefin copolymer pre-filled syringe closed with bromobutyl elastomeric grey tip cap. The container closure system has been described in sufficient detail and the risk assessment approach and the conclusions are endorsed. Relevant studies concerning functionality of the system and compatibility have been conducted. The suitability of the container closure system for its intended use has been adequately demonstrated through development and stability studies. The material complies with Ph. Eur. and EC requirements

The formulation of the batches used in clinical trials is the same as proposed for the intended commercial formulation.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process consists of the following main steps: weighing/compounding, filtration, degassing, filling, terminal sterilisation by gamma irradiation, visual inspection and secondary packaging.

The manufacturing process has been described including process parameters, in-process controls, irradiation procedure, and equipment. Process hold times have been defined and verified in the process validation studies for commercial production. The critical process parameters, in-process controls, and their ranges follow the development studies presented in section P.2 of the dossier and are supported by process validation studies. There are no intermediates in the manufacturing of the finished product.

Process validation results have been requested by CHMP during procedure as a Major Objection. In response, the manufacturing process has been validated with three consecutive, production scale batches. The validation followed the submitted protocol. The process validation data demonstrates that the manufacturing process is robust and reproducible. The predetermined quality attributes as well as in-process controls met their acceptance criteria. The ranges and values selected for the processing parameters are acceptable to support the commercial production.

The sterilisation of the finished product occurs at a different facility from the site responsible for the finished product manufacturer, and it has been shown that the transport conditions do not affect the integrity of the syringes, and therefore, can be considered validated. The suitability of product sterilisation by gamma irradiation has been shown by satisfactory physical and microbiological challenge qualification data.

2.4.3.3. Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance, identification (UHPLC, UV), deliverable weight in container (in house), content uniformity (UHPLC), residual alkyl mesylates (GC-MS), degradation products (UHPLC), water content (KF), particulate matter (Ph. Eur.), average molecular weight by weight of polymer by GPC-RI (in house), average molecular weight by number of polymer GPC-RI (in house), polydispersity by GPC-

RI (in house), breakloose force (in house), glide force (in house), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.), accelerated release *in vitro* (in house), and assay (UHLPC).

The proposed acceptance criteria for the quality attributes are sufficiently justified and acceptable. The specification limits are either in accordance with the Ph. Eur. requirements or they are based on development studies, batch analysis data, and stability data.

The potential presence of elemental impurities in the finished product has been assessed considering requirements specified in the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided on three pilot and six commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

2.4.3.4. Stability

Stability data from three pilot scale and three commercial scale batches of finished product stored for up to 24 months under long term conditions (5 ± 3ºC) and for up to 6 months under accelerated conditions (25ºC / 60% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The samples were tested for all stability indicating parameters included in the specification. The analytical procedures used are stability indicating.

The stability study results show that the finished product is sensitive to heat

Due to the heat sensitivity of the finished product the proposed storage condition of 5 ± 3°C is acceptable.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products and the results show that the finished product is sensitive to light. Therefore, the proposed storage statement "Store in the original package in order to protect from light" is considered acceptable.

Based on available stability data, the proposed shelf-life of 2 years and storage conditions of 'Store in a refrigerator (2°C – 8°C). Store in the original package in order to protect from light.' as stated in the SmPC (section 6.3 and 6.4) are acceptable.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The aim of the pharmaceutical development was to develop a product similar to the reference product Eligard 45 mg powder and solvent for solution for injection, and to have enhanced stability to allow the product to be pre-filled into a single, ready-to use syringe for easier administration.

During the procedure a multidisciplinary major objection on the bridging between the reference product EU-Eligard and Camcevi has been resolved, as well as major objections on proposed specifications for polymer molecular weight and *in vitro* accelerated release, and missing process validation data. All MOs were resolved by the provision the requested information.

The applicant has applied QbD principles in the development of the finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The expected pharmacological effect of Camcevi 42 mg (also LMIS 50 mg), an initial rise in serum testosterone level followed by a continuous suppression of the serum testosterone level below normal

levels, was demonstrated by several single dose subcutaneous (SC) PK/PD studies in male rats. In these studies, different depot formulations of leuprorelin mesilate including formulations from early phase formulation development, but also nonclinical and clinical batches were tested. In the submitted pharmacological study, 4 different leuprorelin mesilate depot formulations were compared to a single SC dose of the leuprorelin acetate reference drug, Eligard (US sourced), and vehicle in male Sprague Dawley rats. A single SC dose of approximately 10.8–12.0 mg leuprorelin mesilate/animal in Camcevi formulations and 9.6 mg leuprorelin acetate/animal in Eligard was injected and animals were observed for 196 days. Mean testosterone levels transiently increased before decreasing below the level of the vehicle control group by Day 7 for all tested leuprorelin formulations. Testosterone levels of rats in all leuprorelin mesilate groups were decreased to close to human castration level (0.5 ng/mL) or below from Day 28 until the end of the study. Comparable suppression of serum testosterone levels between Camcevi and Eligard (US sourced) at equal dose levels were also shown in GLP compliant single dose SC toxicity studies in rats with follow up periods up to 6 months. These studies utilised a Camcevi batch, which was manufactured using the same process as for the GMP clinical batch.

2.5.2.1. Secondary pharmacodynamic studies, Safety pharmacology programme, Pharmacodynamic drug interactions

Secondary pharmacodynamics, safety pharmacology or pharmadynamic drug interaction studies were not performed. These studies are not required since there is very long clinical experience with leuprorelin in the proposed indication, which supersedes animal data and any new findings are not expected.

2.5.3. Pharmacokinetics

The applicant has developed a leuprorelin mesilate ready-to-use injectable suspension (Camcevi 42 mg). Camcevi 42 mg is a pre-mixed product containing leuprorelin mesilate equivalent to 42 mg leuprorelin, which is formulated in a solution of NMP and PLA. The proposed product is formulated to control and sustain the release of the bioactive leuprorelin over a 6-month period after a single SC administration.

The free base equivalent is the same between the proposed Camcevi 42 mg product and the currently approved 45 mg leuprorelin acetate product Eligard 45 mg powder and solvent for solution for injection (Eligard 45 mg), which is used as a reference product in this hybrid application.

During formulation development a 28-week single subcutaneous dose PD/PK comparison study between four different Camcevi 42 mg candidate depot formulations and the reference product Eligard 45 mg was performed in male Sprague-Dawley (SD) rats. A 6-month PK/PD study following a single subcutaneous dose of various preliminary "Design of Experiment (DoE) batches was conducted in male SD rats. A comparative 6-month PK/PD study in male SD rats after a single subcutaneous dose of aged versus new Camcevi 42 mg batches were performed.

Additional PK/PD data were collected from 28-day non-GLP compliant and pivotal GLP_compliant 3- and 6-month single subcutaneous dose toxicity studies in rats. The LC-MS/MS method was developed and validated for the simultaneous determination of leuprorelin and testosterone in rat serum.

No studies were conducted to evaluate biodistribution of leuprorelin mesilate. One literature report on biodistribution of leuprorelin acetate-loaded liposomes labelled with technetium-99m in Ehrlich ascites tumour bearing mice was referenced. This study showed that labelled leuprorelin after intravenous injection was rapidly distributed into the heart, lung, liver and spleen. However, the results of distribution study using leuprorelin acetate-loaded liposomes may not be comparable to distribution of

leuprorelin mesilate from sustained release solution formulated with NMP and PLA administered by subcutaneous route.

No metabolism studies were conducted with Camcevi 42 mg product or leuprorelin mesilate. According to published literature in rats and dogs, ^{14}C-labeled leuprorelin was metabolised by circulating peptidases to smaller peptides, a pentapeptide (Metabolite I), tripeptides (Metabolites II and III) and a dipeptide (Metabolite IV, $pGlu^1$-His^2-OH). Using mouse kidney preparations *in vitro*, two metabolites were detected, the major one being the pentapeptide M–I (Tyr5- D-Leu6-Leu7-Arg8-Pro9-NHC2H5) and the minor metabolite, the tripeptide M–III (pGlu1-His2-Trp3-OH).The major metabolite, M-1 pentapeptide has been identified in both animals and human.

Two lactide-dependent impurities A and B were adequately qualified. The *in vitro* stability of leuprorelin D,L lactide acetate was assessed in comparison to leuprorelin mesilate in whole blood and serum of rats (Sprague-Dawley) and humans. Leuprorelin mesilate was stable in all tested matrices with predicted half-life longer than 231 minutes. Leuprorelin-D, L lactide acetate was unstable in all matrices. The half-life in serum was less than 10 minutes and less than 30 minutes in whole blood.

No excretion studies were conducted with Camcevi 42 mg or leuprorelin mesilate. Published literature suggests that small amounts of leuprorelin and its metabolites are predominantly excreted in the urine.

No studies on pharmacokinetic drug interactions have been conducted with Camcevi 42 mg or leuprorelin mesilate. Leuprorelin is a peptide that is primary degraded by peptidase enzymes without participation of cytochrome P450 enzymes in metabolism. During the long-term clinical use no relevant PK drug interactions have been reported nor are expected.

2.5.4. Toxicology

Single dose toxicity studies

In order to support clinical use and the marketing authorisation application of Camcevi 42 mg, an abbreviated nonclinical programme was completed including a comparative 28-day single dose SC toxicity study in male Sprague Dawley (SD) rats (non-GLP compliant) and comparative pivotal GLP compliant 3- and 6-month single dose subcutaneous toxicity studies in male SD rats.

The same batch of Camcevi 42 mg was used in all three studies (Batch number CC0442, which was manufactured using the same process as for the GMP clinical batch). The Taiwanese test facility that conducted two pivotal single dose subcutaneous toxicity studies in rats that are included in the MAA was not part of an EU or an OECD Mutual Acceptance of Data (MAD) accepted GLP monitoring programme in the period in which the test facility was used.

US-sourced Eligard 45 mg was used as a reference product in the toxicity studies. In addition to three own toxicity studies, SmPC text of Eligard 45 mg and publically available literature was used to provide additional safety information.

All three studies used the same dose groups: Grp 1) sham control (saline), Grp 2) vehicle control (Camcevi vehicle), Grp 3) Camcevi - 6.8 mg/animal of leuprorelin mesilate, Grp 4) Camcevi - 20.3 mg/animal of leuprorelin mesilate, Grp 5) Camcevi - 33.8 mg/animal of leuprorelin mesilate, and Grp 6) Eligard - 30.0 mg/animal of leuprorelin acetate. Expressed in amount of leuprorelin base, animals from groups 3-6 received a dose of 5.8, 17.4 29.0 and 28.0 mg/animal, respectively. Considering rats with 250 g body weight, these doses of leuprorelin correspond to 23.2, 69.6, 116 and 112 mg/kg of

leuprorelin, respectively. For comparison, the clinical dose of 42 mg given to a patient with 60 kg body weight corresponds to 0.7 mg/kg of leuprorelin.

In a 28-day single SC dose-range finding study in male SD rats (non-GLP), the primary target organs of leuprorelin were testes and epididymides, affecting prostate/seminal vesicles. Changes related to the reduced testosterone level included reduced red blood cell levels and increased prothrombin time.

In a pivotal 3-month single dose SC toxicity study there was no significant difference in systemic drug exposure between Camcevi 42 mg and Eligard 45 mg in male rats. SC injection of Camcevi 42 mg and Eligard 45 mg induced initial increase of serum testosterone during 3 days or less at all groups (Groups 3 - 6) followed by reduction of serum testosterone. Serum testosterone level was below castrate level (≤ 0.5 ng/mL) during the last 2 months or more of the 3-month implantation period with sporadic higher level than castrate level but at or below 0.8 ng/mL. The following Camcevi 42 mg-related changes were noted: a) shortening of prothrombin time (PT); b) reduced size and/or weights of kidney and male sex organs (testes, epididymides, prostate and seminal vesicles); and c) hyperplasia in pituitary, which were also noted in the Eligard 45 mg group. Shortened PT (9 to 12% compared to vehicle control group) was noted in all Camcevi 42 mg groups with a dose dependent manner and in Eligard 45 mg group with similar severity. Changes in testes and epididymides were considered to be primary changes that caused secondary changes in prostate and seminal vesicles. The NOAEL of Camcevi 42 mg was below 6.8 mg leuprorelin mesilate/animal since pituitary hyperplasia was still noted at this level. Male SD rats of 7 weeks old at the first dosing were used. At this age the rats are sexually but not socially matured, and this age of rats corresponds to very young human. From anatomical and physiological point of view, the older rats may have been a better animal model of the older men, the main target patients of the product.

In a pivotal 6-month single SC dose toxicity study in male rats, the C_{max} and $AUC_{0\text{-}182day}$ of leuprorelin increased proportional to dose in the Camcevi 42 mg treated groups. Both Camcevi 42 mg and Eligard 45 mg reduced serum testosterone levels to the castrate level (≤ 0.5 ng/mL) starting on Dosing Days 15 and 22 and similarly lower serum testosterone levels were maintained until termination on Dosing day 183. Leuprorelin caused significant changes in the pituitary characterised histologically as focal hyperplasia and/or adenoma that contributed to the gross findings (enlargement, nodule and masses) and increased weight. There was apparently higher incidence of pituitary adenomas in animals treated with Camcevi compared to Eligard. The number of animals with pituitary adenomas in groups 1, 2, 3, 4, 5 and 6 (corresponding to sham control, vehicle control, Camcevi 6.8 mg/animal, Camcevi 20.3 mg/animal, Camcevi 33.8 mg/mal and Eligard 30.0 mg/animal, respectively) were 0, 0, 8, 5, 8 and 4, respectively. It is reported in the literature that focal hyperplasia in the pituitary is the precursor of adenoma in rat brain. The pituitary changes led to worsened clinical condition of three animals seen as decreased activity and dehydration. One animal was sacrificed before scheduled termination due to these clinical signs. As a result of reduced testosterone levels, reduced weights of size in male sex organs, germ cell depletion in testis, reduced luminal sperm in epididymis and decreased luminal secretions in prostate and seminal vesicles were observed. Reduced weight in the heart, liver and kidney without related gross and histopathologic findings were evident. Coagulation changes characterised as shortened PT (-21 to -24%) without changes in activated partial prothrombin time were observed. The NOAEL was below 6.8 mg leuprorelin mesilate/animal since the pituitary changes such as hyperplasia or adenoma noted at this level and higher were considered to be adverse. Also in this long-term study very young, though sexually matured rats (9 weeks age at the start of the study) were used.

Repeat dose toxicity

No repeat-dose toxicity studies were performed with Camcevi 42 mg. To prove the absence of genotoxicity the SmPC of Eligard was referred to.

Reproduction toxicity, Fertility and early embryonic development

Studies evaluating effects on fertility and early embryonic development with Camcevi 42 mg have not been performed.

Separate studies evaluating effects of Camcevi 42 mg on embryo-foetal development have not been conducted. Camcevi 42 mg is contraindicated in women. No studies evaluating effects of Camcevi 42 mg on pre- and postnatal development (including maternal function) have been performed. Camcevi 42 mg is contraindicated in paediatric patients, therefore no studies in juvenile animals have been conducted.

Local Tolerance

Local tolerance assessment was performed in single-dose subcutaneous 6-month toxicity study in rats. No significant differences in histopathological findings in injection site were evident between Camcevi 42 mg and Eligard 45 mg.

Other toxicity studies

The proposed Camcevi 42 mg formulation contains the solvent N-methylpyrrolidone (NMP). Each single sterile, pre-filled syringe contains 139.40 mg NMP/syringe (37.68%) as a solvent.. The published preclinical studies have shown that following intravenous or intraperitoneal administration the substance was extensively distributed to all major organs and the highest accumulation was detected in the liver, muscle, intestines, fat tissue and testicles. The no observed adverse events levels (NOAELs) of NMP in rodent repeat-dose toxicity studies were significantly higher on mg/kg basis than the amount of NMP in a single Camcevi 42 mg dose. No comparison between animal and human NMP exposures was made. In the literature there are reports showing that the ability to accumulate NMP and/or its metabolites in testes and seminal vesicles may be the reason for fertility impairment in male rats observed after repeated oral exposure to this compound (Sitarek and Stetkiewicz 2008, Sitarek and Kilanowicz 2006). ICH Q3C classifies NMP as Class II solvent and limits its use with PDE of 5.3 mg/day due adverse neurodevelopmental effects after in utero exposure to this chemical. A separate risk assessment for use of NMP at the level present in Camcevi 42 mg and specially, for potential NMP-related gonadotoxicity in Camcevi 42 mg was provided. No risk for male reproductive toxicity is anticipated with the current level of use of NMP in the drug product Camcevi 42 mg due to a rapid elimination of NMP and once in six-month dosing of the product. The Camcevi-related effects on male reproductive organs are consistent with the expected pharmacology of leuprorelin, the reduction of the testosterone level.

2.5.5. Ecotoxicity/environmental risk assessment

Leuprorelin is a synthetic nonapeptide, which is degraded to inactive peptide fragments prior to excretion in small amount in the urine. In line with EMEA/CHMP/SWP/4447/00 Rev. 1; leuprorelin is readily biodegradable and therefore it is not expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

The applicant has developed a leuprorelin mesilate injectable suspension 50 mg. Camcevi 42 mg (LMIS 50 mg) prolonged-release suspension for injection is indicated for the treatment of advanced prostate cancer.

The legal basis of this marketing authorisation application is a hybrid application. Since a clinical pharmacokinetic/pharmacodynamic bridge was established between Camcevi 42 mg and different leuprorelin medicinal products from the EU and USA, rely on relevant information presented in the SmPC of the proposed reference medicinal product EU-Eligard can be acceptable. In order to further support the marketing authorisation application of Camcevi 42 mg the published literature was reviewed for additional supportive information. To obtain a complete and current update on the published literature covering any significant findings obtained of the leuprorelin, repeated searches in a variety of classified databases were performed (up to October 2020). Amongst the 493 publications found, 15 selected articles showing the anti-tumor effects of the leuprorelin especially for the prostate cancer, pharmacokinetics, and toxicology (antigenicity) of leuprorelin were included in the respective updated sections in Module 2.4 Non-clinical Overview.

A very restricted nonclinical programme with the Camcevi 42 mg was conducted. No separate absorption studies were performed. Several studies were conducted to characterise the PK/PD relationship during Camcevi 42 mg formulation development and to demonstrate durable pharmacological efficacy in terms of reducing the testosterone level to castrate levels. No studies on secondary pharmacodynamics, safety pharmacology or pharmacodynamics interactions were conducted, which is acceptable as leuprorelin is a well-established compound in the proposed indication.

No studies on distribution, metabolism, excretion or pharmacokinetic drug interaction were conducted. Given its decades of use in the proposed indication, sufficient clinical information is available which supersedes animal data. A study in mice showed that radiolabelled leuprorelin after intravenous injection was rapidly distributed into the heart, lung, liver and spleen. However, there are no experimental data available on distribution of leuprorelin mesilate from sustained release solution formulated with the excipients NMP and PLA and administered by subcutaneous route.

Three single dose SC toxicity studies in male SD rats were performed: non-GLP 28-day single dose range-finding study, followed by GLP 3-month single dose and 6-month single dose toxicity studies. Very young, though sexually mature rats were used in the toxicity studies instead of more mature males. According to the applicant this allowed the comparison to the broad database of historical control values supporting the determination of drug toxicities which are dependent on the ability to distinguish spontaneous events from the toxicological ones. Variability between the individual aged rats and the lack or little historical control data would require the use of higher number of animals per group in the GLP toxicity study. In both 3- and 6-month toxicity studies leuprorelin showed expected toxicities which were related to the pharmacological action of this class of compounds and which were comparable to similar medicinal drug products such as Eligard.

All three studies used the same dose groups. Expressed in amount of leuprorelin base, animals from groups 3-6 received a dose of 5.8, 17.4 29.0 and 28.0 mg/animal, respectively. Considering rats with 250 g body weight, these doses of leuprorelin correspond to 23.2, 69.6, 116 and 112 mg/kg of leuprorelin, respectively. For comparison, the clinical dose of 42 mg given a patient with 60 kg body weight corresponds to 0.7 mg/kg of leuprorelin. A main reason for the dose selection was to achieve systemic exposures of leuprorelin in rat toxicity studies which were sufficiently above systemic exposures in patients. Moreover, for a very viscous formulation such as Camcevi 42 mg, it was not possible to inject very small volumes or weights. In addition, very small volumes were not considered

adequate for depot formation, as a result, sustained release property could not be well maintained to mimic human applications. The margins derived from comparison of systemic exposure in animals compared to systemic exposures in humans ranged from 0.3 to 3 in terms of C_{max} and from 1 to 17 in terms of AUC, which confirms adequacy of selected doses to evaluate potential toxicities of Camcevi 42 mg.

The two pivotal long-term (3 and 6 months) toxicity studies have a GLP compliance issue. According to the information provided in the *EMA Non-clinical studies GLP compliance* (*Annex to the cover letter*) the test facility located in Taiwan was not part of an EU or an OECD Mutual Acceptance of Data (MAD) accepted GLP monitoring programme in the period in which the test facility was used. However, as a hybrid application is in question, a GLP inspection was not considered necessary, and referring to the non-clinical data of the reference medicinal product is sufficient.

No repeat-dose toxicity studies were conducted. Camcevi 42 mg is prolonged-release product and effects of continuous release of leuprorelin were observed for up to 6 months in male rats. It is agreed that repeat-dose study would not have provided any new relevant information about the product's safety.

No genotoxicity studies were performed. References to the SmPC of Eligard 45 mg, which informs about the absence of mutagenicity of leuprorelin in *in vitro* and *in vivo* assays, were made. No carcinogenicity studies have been performed with Camcevi 42 mg. However, leuprorelin containing medicinal products have been in clinical use for decades and formulation changes in Camcevi 42 mg (excipients, salt, *etc*.) do not constitute any additional carcinogenic risk. Thus, using weight of evidence approach, it is considered acceptable to refer to the data and SmPC of the reference medicinal product.

In the 6-month single-dose SC study the number of animals with pituitary adenomas in groups 1, 2, 3, 4, 5 and 6 (corresponding to sham control, vehicle control, Camcevi 6.8 mg/animal, Camcevi 20.3 mg/animal, Camcevi 33.8 mg/animal and Eligard 30.0 mg/animal, respectively) were 0, 0, 8, 5, 8 and 4, respectively. It is reported in the literature that focal hyperplasia in the pituitary is the precursor of adenoma in rat brain. The combined incidence of pituitary hyperplasia and adenoma in the Camcevi-treated groups was comparable to the Eligard-treated group and thus, the risk to develop adenoma due to leuprorelin exposure is considered the same between the two products.

No published study related to leuprorelin's antigenicity could be identified in the literature search. However, information on animal studies evaluating the antigenicity of leuprorelin was found in a Canadian Product monograph and a Public Assessment Report for a leuprorelin containing medicinal product. Based on the provided data leuprorelin does not have antigenic potential.

There are no studies evaluating effects on fertility, early embryonic development and embryo-foetal development. The information concerning adverse effects of leuprorelin on the reproductive system, particularly impairing male fertility are reflected in SmPC sections 4.6 and 5.3 in alignment with the reference product.

The proposed Camcevi 42 mg formulation contains the solvent NMP. The reported preclinical studies in the literature have shown that following intravenous or intraperitoneal administration the substance extensively distributed to all major organs and the highest accumulation was detected in the liver, muscle, intestines, fat tissue and testicles. The NOAELs of NMP in rodent repeat-dose toxicity studies were significantly higher on mg/kg basis than the amount of NMP in a single Camcevi 42 mg dose. No comparison between animal and human NMP exposures was made. In the literature there are reports showing that the ability to accumulate NMP and/or its metabolites in testes and seminal vesicles may be the reason for fertility impairment in male rats observed after repeated exposure to this compound. In addition, changes in testes and epididymides were reported in long-term single dose toxicity studies

in rats with Camcevi 42 mg. A separate risk assessment for use of NMP at the level present in Camcevi 42 mg and specially, for potential NMP-related gonadotoxicity in Camcevi 42 mg was provided during the procedure. No risk for male reproductive toxicity is anticipated with the current level of use of NMP in the drug product Camcevi 42 mg due to a rapid elimination of NMP and once in six-month dosing of the product. The effects on male reproductive organs following long-term Camcevi 42 mg exposure in rats are consistent with the expected pharmacology of leuprorelin, the reduction of the testosterone level.

Leuprorelin is a synthetic nonapeptide, which is degraded to inactive peptide fragments by circulating peptidase enzymes prior to excretion in the urine. No specific ERA studies are required for the active substance leuprorelin.

2.5.7. Conclusion on the non-clinical aspects

Overall, the non-clinical package is considered adequate to support a hybrid application. The relevant sections of the SmPC are aligned with the reference product.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Study ID **Number of Study Centres** **Location(s)**	**Design** **Control Type** **Study start** **Enrollment status, data** **Total enrollment/ enrollment goal**	**Study & Control Drugs Dose, Route & Regimen**	**Study Objective** **Duration** **Gender M/F** **Median Age (Range)**	**Diagnosis Inclusion Criteria**	**Efficacy Evaluation**
FP01C-13-001 26 Austria, Czech Republic, Germany, Lithuania, Poland, Slovakia, Taiwan, United States	Open-label, single-arm 12 Aug 2014 Completed 2 Sep 2016 137/133	2 injections of LMIS 50 mg given SC at 6 months apart	PK, efficacy and safety 1 year 137/0 71.0 (51, 88)	Males ≥ 18 years old with histologically confirmed carcinoma of the prostate with baseline serum testosterone level > 150 ng/dL	Percentage of patient with serum testosterone levels ≤ 50 ng/dL by Day 28 (± 1 day) Percentage of patients with serum testosterone levels ≤ 50 ng/dL from Day 28 through Day 336

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The pharmacokinetics of leuprorelin has been investigated in the clinical Study FP01C-13-001. Patients with advanced prostate cancer in need of androgen ablation were included in this Phase 3, multicentre, uncontrolled, open-label, single-arm, 12-month study. The study included two parts (Part I: n=33, Part II: n=104). One hundred thirty one (131) male subjects had evaluable PK data. The majority of the patients were white (90%) with a mean age of 71 years, with a mean body weight of 86 kg and a baseline serum testosterone level of 4.72 ng/mL. Serum concentrations of leuprorelin, testosterone (PD measurement) and LH (PD measurement) were analysed using validated LC-MS/MS bioanalytical methods.

Pharmacokinetics of leuprorelin after LMIS 50 mg was characterised by two phases and rapid increase of serum leuprorelin concentrations. Peak concentrations of about 90 ng/mL were reached about 2-4 hours after injection. After the rapid burst concentrations declined rapidly during the next three days after dosing. In Part I mean concentrations of 3.18 and 4.23 ng/mL on Day 3 and Day 171 following the first and second doses were observed, respectively. The corresponding mean concentrations in Part II, Day 3 and Day 171 were 3.78 ng/mL and 3.94 ng/mL following the first and second doses, respectively. Mean serum concentrations at plateau phase through the six-month dosing interval ranged between 0.370 to 2.97 ng/mL. Although a slight increase in leuprorelin concentrations was observed 2-3 months after dosing of LMIS 50 mg, the concentrations remained within the therapeutic window and are minor compared to the peak concentrations observed right after dosing.

Modelling

LMIS is a depot formulation from which leuprorelin is released slowly over 6 months. The reference product is Eligard 45 mg powder and solvent for solution for injection. No formal bioequivalence studies between Eligard and LMIS have been conducted. However, two modelling reports were included in the MAA, Study FSEE-CSC-100 and Study FSEE-PMX-FP001-1605.

The objective of FSEE-CSC-100 was to compare the levels of leuprorelin data obtained following administration of a repeated LMIS 50 mg dose in Study FP01C-13-001 to steady-state levels of leuprorelin following repeated 1 mg intravenous injection of Lupron data obtained from the literature.

Based on the comparison, the exposure to leuprorelin at steady state was approximately five times higher for Lupron than from LMIS. The overall exposure ($AUC_{0\text{-}6mon}$) of leuprorelin was significantly lower for LMIS 50 mg, as well as the absolute C_{max}.

The objective of FSEE-PMX-FP001-16 report was to compare the pharmacokinetics and pharmacodynamics in humans following administration of LMIS and other subcutaneous leuprorelin acetate formulation.LMIS 50 mg was compared with the marketed depot products, namely US-sourced Eligard 45 mg 6M, US-sourced Eligard 22.5 mg 3M (2 consecutive injections of Eligard 3M), EU-sourced Lucrin 22.5 and 30 mg 6M and six consecutive injections of US-sourced Eligard 7.5mg 1M.

The simulation studies provide support for linking the LMIS to the clinical results of marketed depot formulations, and to the original nonclinical and clinical results of Lupron 1 mg IV formulation. The simulation studies did not, however, establish bioequivalence to any of the compared products.

Differences in analytical methods, clinical trial design and conduct of the studies and subject demographics were limitations to this literature-based bridging exercise.

The comparison exercise was considered valuable for the bridging of safety, both to the IV formulation and to the depot formulations. For Lupron 1mg IV formulation, both the C_{max} and the $AUC_{0\text{-}6\ mon}$ are much higher than they are for LMIS 50 mg, and therefore safety can be bridged from Lupron 1mg.

The data used for simulations for Eligard and Lupron are from FDA approval packages. Data for Lucrin is obtained from an assessment report of Netherlands Medicines Evaluation Board.

Absorption

Leuprorelin is released continuously by the third day after dosing with steady serum concentrations ("plateau" phase) through the 24-week (approximately 6-month) dosing interval (mean concentration: 0.370 to 2.97 ng/mL).

Peak leuprorelin concentrations occurred about 2 to 4 hours after the LMIS injection. Three days after the dose mean leuprorelin levels were approximately 2 to 4 ng/ml, thereafter they declined even further. After the initial burst, the drug substance was released slowly from the polymer complex for six months. Six months after the injection leuprorelin concentrations were still sustained within the levels of 0.2-2 ng/ml.

Distribution

The distribution of leuprorelin after subcutaneous administration of LMIS 50 mg has not been investigated in the current documentation.

Elimination

Elimination and excretion of leuprorelin following subcutaneous administration of LMIS 50 mg have not been specifically investigated, and no drug excretion study was conducted with leuprorelin.

Pharmacokinetics in the target population

In the clinical study FP1C-13-001 LMIS 50 mg was administered as two injections six months apart from each other to patients with advanced prostate carcinoma.

The mean C_{max} value of serum leuprorelin was around 94-100 ng/mL and it was reached after approximately 2-4 hours after the first and the second dose of LMIS 50 mg injections. The concentrations declined rapidly after reaching the peak and the mean level of 3.18-4.23 ng/ml was seen three days after dosing. The concentrations declined further after this and the mean plasma concentrations at 4 weeks were 1.04-2.4 ng/ml. However, in some subjects leuprorelin concentrations increased again 2 or 3 months after dosing.

Table 1. Summary of serum pharmacokinetic parameters of leuprorelin after LMIS 50 mg subcutaneous injections in Part I

PK Parameter	First Dose			Second Dose		
	N	Mean	SD	N	Mean	SD
C_{max}, ng/mL	31	94.5	53.7	29	99.0	73.0
T_{max}, h	31	3.23 (1.17, 7.90)		29	2.08 (1.17, 8.00)	
C_{wk4}, ng/mL	31	1.04	0.863	29	1.64	0.983
C_{mon6}, ng/mL	29[a]	0.497	0.610	29	0.511	0.488
$AUC_{0\text{-}4wks}$, day·ng/mL	31	91.6	47.9	29	125	57.3
$AUC_{0\text{-}6mon}$, day·ng/mL	29[a]	224	87.3	29	268	88.1
$C_{avg(0\text{-}6mon)}$, ng/mL	29[a]	1.34	0.519	29	1.59	0.525

[a] two subjects' PK parameters were not reportable

$AUC_{0\text{-}4wk}$ = area under the concentration-time curve from time 0 to 4 weeks post-dosing; $AUC_{0\text{-}6mon}$ = area under the concentration-time curve from time 0 to 6 months post-dosing; $C_{avg(0\text{-}6mon)}$ = mean serum concentration within 6 months post-dosing; C_{max} = maximum serum concentration; C_{wk4} = plasma concentration at 4 weeks post-dosing; C_{mon6} = plasma concentration at 6 months post-dosing; N = number of subjects; PK = pharmacokinetics; SD = standard deviation; T_{max} = time to reach maximum serum concentration;

Figure 2. Arithmetic mean leuprorelin and testosterone serum concentration-time after LMIS 50 mg SC Injections to male subjects with advanced prostate carcinoma at Part I of the study

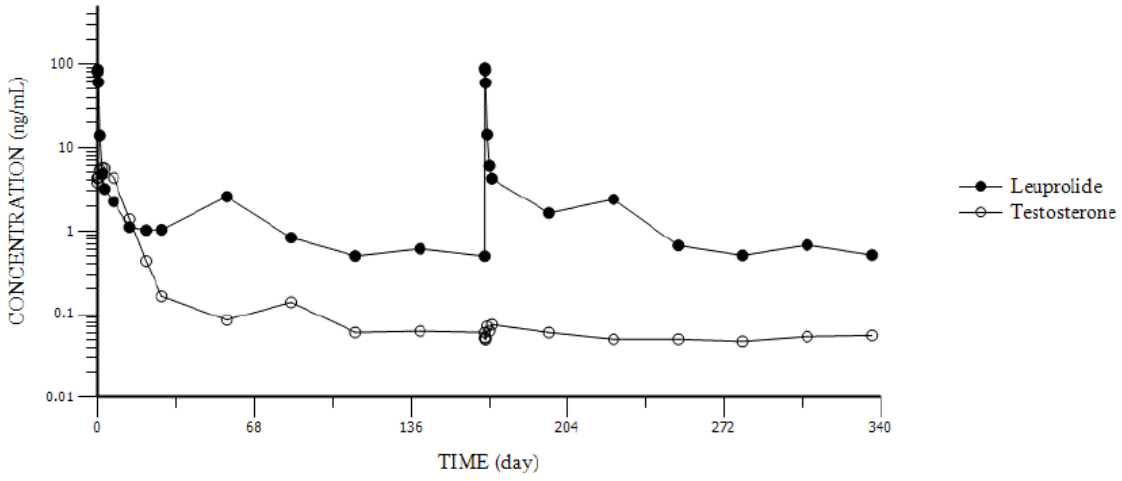


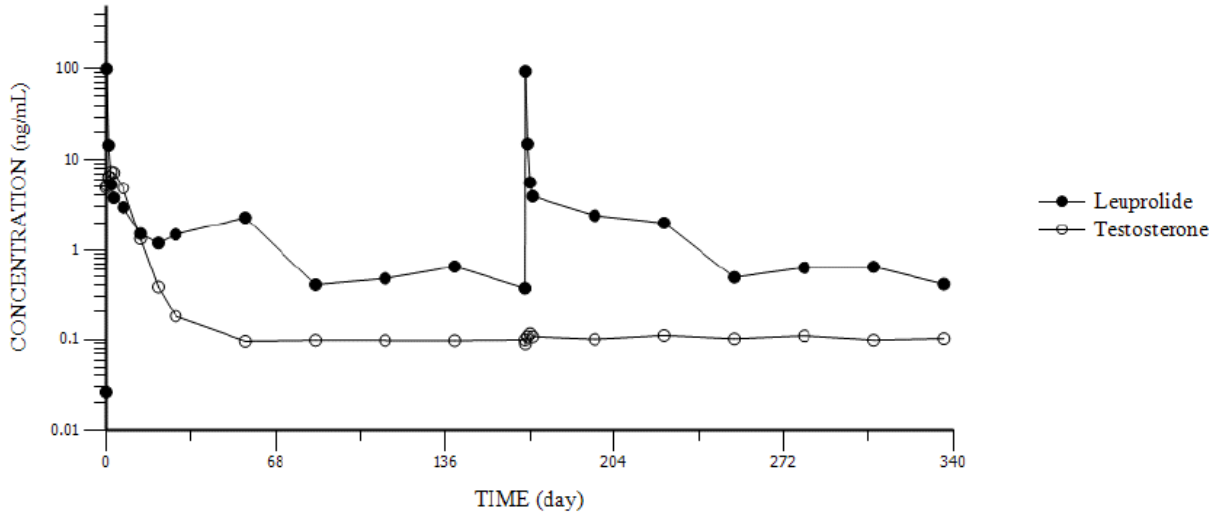
Table 2. Summary of serum pharmacokinetic parameters of leuprorelin after LMIS 50 mg subcutaneous injections in Part II

	First Dose			Second Dose		
PK Parameter	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
C_{max}, ng/mL	94	99.7	65.6	97	93.7	60.8
T_{max}, h[a]	94	3.67 (2.83, 24.00)		97	3.78 (2.87, 5.17)	
C_{wk4}, ng/mL	94	1.47	2.57	96[b]	2.40	4.05
C_{mon6}, ng/mL	92[a]	0.370	0.313	94[b]	0.410	0.538
$AUC_{0\text{-}4wks}$, day·ng/mL	94	103	62.4	96[b]	131	91.4
$AUC_{0\text{-}6mon}$, day·ng/mL	92[a]	219	108	94[c]	250	160
$C_{avg(0\text{-}6mon)}$, ng/mL	92[a]	1.31	0.643	94[c]	1.49	0.950

[a] not reportable for 2 subjects; [b] not reportable for 1 subject; [c] not reportable for 3 subjects

$AUC_{0\text{-}4wk}$ = area under the concentration-time curve from time 0 to 4 weeks post-dosing; $AUC_{0\text{-}6mon}$ = area under the concentration-time curve from time 0 to 6 months post-dosing; $C_{avg(0\text{-}6mon)}$ = mean serum concentration within 6 months post-dosing; C_{max} = maximum serum concentration; C_{wk4} = plasma concentration at 4 weeks post-dosing; C_{mon6} = plasma concentration at 6 months post-dosing; PK = pharmacokinetics; SD = standard deviation; T_{max} = time to reach maximum serum concentration

Figure 3. Arithmetic mean leuprorelin and testosterone serum concentration-time after LMIS 50 mg SC injections to male subjects with advanced prostate carcinoma at Part II of the study



Special populations

Over 90 % of the patients included in the clinical studies were white (Caucasians). Only few patients with other ethnic background were studied. The plasma concentration data between white, black, Asian and other are similar.

Serum leuprorelin concentrations were decreased in patients over 100 kg. Overall serum leuprorelin exposure over the first four weeks following LMIS 50 mg administration was decreased by 42%, while exposure over six months was decreased by 20% in subjects >100 kg compared to subjects <75 kg. Significant differences related to subjects' body weight were observed for serum leuprorelin peak concentration and exposure during the first 4 weeks post-dose ($p \leq 0.03$).

Table 3 summarises the number of patients studied at different age strata.

Table 3. Proportion of age strata among elderly patients in main study FP01C-13-001

Study	Age 65-74 (Older patients number/total number)	Age 75-84 (Older patients number/total number)	Age 85+ (Older patients number/total number)
FP01C-13-001 (LMIS 50 mg, N=131)	51/137 (37.2%)	45/137 (32.8%)	6/137 (4.38%)

Pharmacokinetic interaction studies

No interactions studies have been performed with LMIS.

2.6.2.2. Pharmacodynamics

Mechanism of action

Leuprorelin is a synthetic nonapeptide analogue of naturally occurring GnRH that, when given continuously at therapeutic doses, inhibits pituitary gonadotropin secretion and suppresses testicular and ovarian steroidogenesis. Initial administration of leuprorelin causes an increase in gonadotropin levels (LH, FSH, leading to a transient rise in gonadal steroid production). For this reason, the concomitant use of an anti-androgen is recommended in male patients as anti-androgen flare protection. With continuous administration, there is eventual suppression of gonadotropin release within 2 to 4 weeks. In males, testosterone is reduced to castrate levels (below the castrate threshold or ≤ 50 ng/dL). Upon removal of the drug, this effect is reversible. The biological effect of the GnRH agonist leuprorelin is time- and not concentration-dependent.

LMIS 50 mg is supplied as a ready-to-use pre-filled syringe.

Primary and Secondary pharmacology

Independent pharmacodynamics (PD) studies were not performed for the current hybrid application since the PD of leuprorelin are known and several leuprorelin-containing products are available in EU. However, the Phase 3 evidence of comparative efficacy was primarily based on testosterone level and secondarily on PSA and LH level measurements. For further evaluation of these aspects, see Section on Clinical efficacy.

Profiles for testosterone after administration of LMIS 50 mg depo, and after administration of Eligard 45 mg depot are shown below.

Figure 4. Arithmetic mean leuprorelin and testosterone serum concentration-time after LMIS 50 mg sc injections in part I of study FP01C-13-001

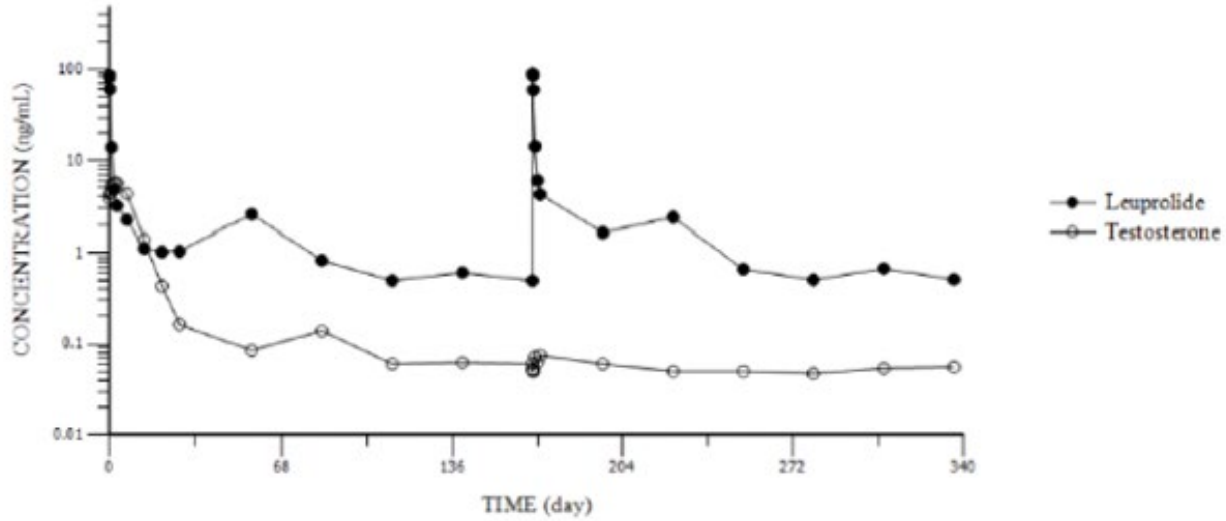
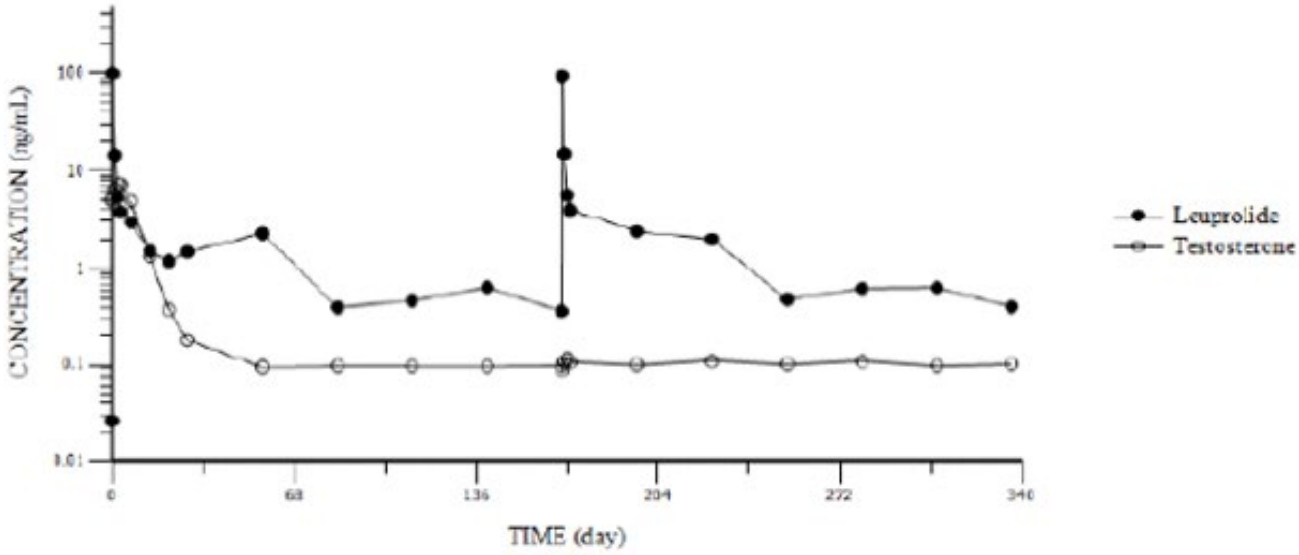
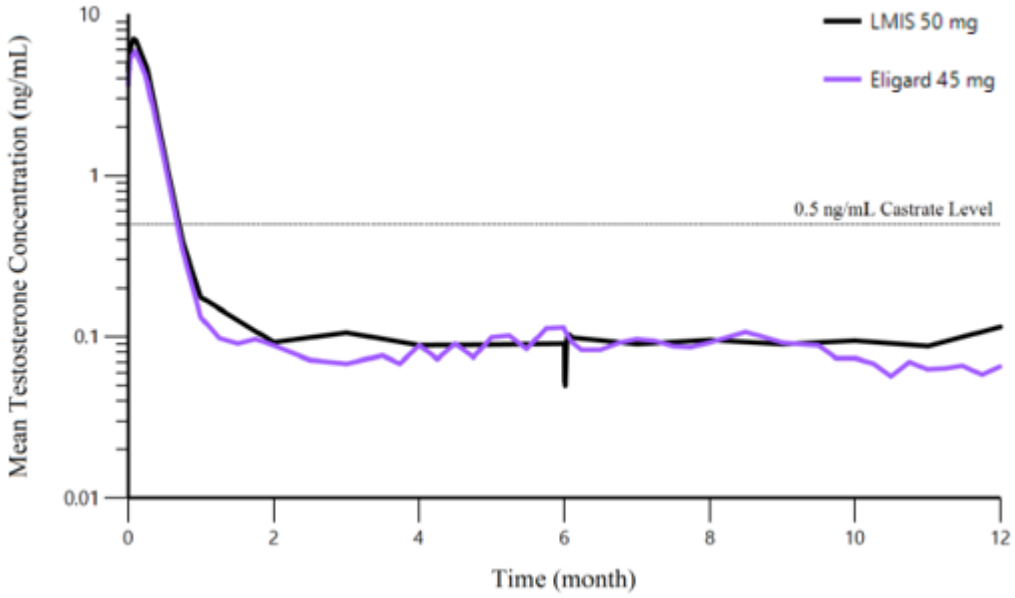


Figure 5. Arithmetic mean leuprorelin and testosterone serum concentration-time after LMIS 50 mg sc injections in part II of study FP01C-13-001



The time to reach the Leuprolide therapeutic window (0.2 – 2 ng/mL) for LMIS 50 mg and Eligard 45 mg was 9.8 and 5.1 days, respectively. The time to reach the castration threshold (0.5 ng/mL) for LMIS 50 mg and Eligard 45 mg was 20.2 and 19.1 days, respectively. See Figure 6.

Figure 6. Mean testosterone profile after administration of LMIS 50 mg 6M and Eligard 45 mg 6M formulations



The observed acute increases of serum testosterone concentration were associated with rapid increases in serum leuprorelin concentrations. Mean serum testosterone concentration increased from a mean baseline value of 380 and 492 ng/dL to a peak of 562 and 739 ng/dL within 2 days during this initial phase for the Part I and II of Study FP01C-13-001, respectively. With continuous serum leuprorelin exposure, the high mean serum testosterone concentration decreased over-time to reach a very low plateau concentration (approximately Week 4) that was maintained through the end of the study. At the end of each dosing period (24 weeks, approximately 6 months after each injection), the majority of subjects had quantifiable leuprorelin concentrations (Study FP01C-13-001).

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics of leuprorelin has been investigated in one clinical study after LMIS 50 mg (Study FP01C-13-001). Patients with advanced prostate cancer in need of androgen ablation were included in a Phase 3, multicentre, uncontrolled, open-label, single-arm, 12-month study performed in two Parts (Part I: n=33, Part II: n= 104). One hundred thirty one (131) male subjects had evaluable PK data. The study indicates that PK of leuprorelin was characterised by two phases and rapid increase of serum leuprorelin concentrations. Peak concentrations of about 90 ng/mL were reached about 2-4 hours after injection. After the initial burst, concentrations declined rapidly during the next three days after dosing. Thereafter the drug substance was released slowly from the polymer complex for 6 months reaching mean plateau serum concentrations of 0.370 to 2.97 ng/ml through the 24-week (approximately 6-month) dosing interval. Six months after the injection leuprorelin concentrations were sustained within the levels 0.2-2 ng/ml.

No formal bioequivalence studies between LMIS 50 mg and the reference product Eligard 45 mg powder and solvent for solution for injection have been conducted. A comparison of LMIS 50 mg with data of the marketed leuprorelin depot products, namely Eligard 45 mg 6M, Eligard 22.5 mg 3M (2 consecutive injections of Eligard 3M), Lucrin 22.5 and 30 mg 6M and six consecutive injections of Eligard 7.5mg 1M was conducted.

Leuprorelin concentrations after repeated LMIS 50 mg dose were also compared to simulated steady-state levels of leuprorelin following repeated daily 1 mg intravenous injection of Lupron obtained from the literature.

The comparisons were considered valuable for the bridging of safety, both to the IV formulation and to the depot formulations. The data used in the simulations of Eligard and Lupron were obtained from FDA Approval Package. The data for Lucrin were from Netherlands Medicines Evaluation Board assessment report. The marketing authorisation for US- and EU-Eligard is based on the same clinical studies, and the dissolution profiles of the EU-and US-sourced Eligard are similar so the PK data of US-sourced Eligard 45 mg 6M can be compared with LMIS 50 mg.

Bioanalytics

Three bioanalytical methods were used for determination of leuprorelin, testosterone and luteinising hormone in serum samples from clinical studies. A LC-MS/MS (liquid chromatography with tandem mass spectrometry) bioanalytical method used for determination of the concentration of leuprorelin in human serum. LC-MS/MS bioanalytical method was also used for determination of testosterone in serum. For determination of luteinising hormone (LH) in human serum a commercial chemiluminescense ELISA (enzyme linked immunosorbent assay) method was used. The analytical methods used are acceptable.

Distribution

The proposed SmPC text is according to the reference product Eligard and is as follows:

- The mean steady-state volume of distribution of leuprorelin following intravenous bolus administration to healthy male volunteers was 27 litres. *In-vitro* binding to human plasma proteins ranged from 43% to 49%.

The volume of distribution estimated after subcutaneous injection has not been stated in the SmPC.

Elimination

The proposed text to the SmPC is based on published data and is as follows:

In healthy male volunteers, a 1 mg bolus of leuprorelin acetate administered intravenously revealed that the mean systemic clearance was 8.34 l/h, with a terminal elimination half- life of approximately three hours based on a two-compartment model. No excretion studies have been conducted with leuprorelin

The pharmacokinetic section of SmPC resembles the product information for the reference product Eligard. The figures for absorption are taken from the clinical study FP01C-13-001 Part II.

PK in target population

LMIS 50 mg has been administered as two injections 6 months apart from each other to patients with advanced prostate carcinoma. The peak concentrations (C_{max}) about 90 ng/ml (arithmetic mean) and median T_{max} 3.67 hours were similar between the two periods. The concentrations declined rapidly after reaching the peak and the mean level of 3.18-4.23 ng/ml was seen three days after dosing. The concentrations declined further after this and the mean plasma concentrations 4 weeks were 1.04-2.4 ng/ml. However, in some subjects leuprorelin concentrations increased again 2 or 3 months after dosing but the second peaks are mostly within the therapeutic dose range. The total exposure of leuprorelin at 6 months ($AUC_{0\text{-}6mon}$), average concentration at 6 months and total exposure over 4-week dosing (AUC_{wk4}) were significantly increased in Period 2 compared to Period 1. However, the concentrations decreased to similar levels 6 months after dosing in both Period 1 and Period 2; thus,

no accumulation is expected. The moderate to high intra- and inter-subject variability in PK parameters is not expected to have any effect on PD endpoints, given the wide therapeutic index of leuprorelin.

Special populations

Serum leuprorelin concentrations are decreased in patients over 100 kg. However, leuprorelin concentrations are within the therapeutic dose range and testosterone levels are below the castrate level in all weight groups, so efficacy is achieved also in patients >100 kg with LMIS 50 mg dose.

Age increased the exposure of leuprorelin. Exposure measured as $AUC_{0\text{-}6mon}$ and concentrations six months after dosing were about two-fold in patients over 79 years compared to patients under 60 years. However, the C_{max} and AUC parameters observed in the elderly are below the C_{max} and AUC observed after Lupron 1 mg IV administration, and safety has been established for Lupron 1mg. Therefore, no safety issues arising from leuprorelin overexposure are foreseen for the elderly.

Pharmacokinetics has not been investigated in subjects with impaired renal or impaired hepatic function. LMIS treatment is intended for men. PK data in women and children are not available as LMIS is contraindicated in women and children.

Interactions

No interactions studies have been performed with LMIS. No pharmacokinetic based interactions are expected as leuprorelin is degraded by peptidase and not by cytochrome P-450 enzymes and the drug is only about 43-49% bound to plasma proteins.

Pharmacodynamics

Contrary to the results on the evaluation of the primary endpoint where testosterone levels below 50 ng/mL were obtained in a similar magnitude and time points as the reference product and literature values, the same appears not to be translated to PSA levels. In several of the time points measured PSA levels remained above the threshold of 4 ng/mL. Furthermore, 6 months after administration of the second dose of LMIS 50 mg, a rise in mean serum PSA levels was observed from Day 252 to Day 336 and did not reach PSA nadirs as low as evidenced in the referenced studies. Additionally, percentage of change in PSA level from baseline to Day 336 was higher for Eligard than for LMIS (97% and 89%, respectively).

It is pharmacologically and therapeutically plausible that the higher PSA nadir obtained in study FP01C-13-001 (>4ng/mL), and the rise in PSA levels in the end of the follow-up period, was based on the higher PSA levels at baseline compared to the Eligard and other studies, as well as differences in patient recruitment leading to patients with higher disease severities and the existence of castration resistant prostate cancer patients contributing to higher mean PSA levels at the end of the follow-up period.

Details for the first days after the first dose of Eligard 45 mg were provided (data not shown). After the first dose of LMIS 50 mg or Eligard 45 mg, the C_{max} of the mean profiles were 95.4 and 79.5 ng/mL, respectively. C_{max} occurred at 4 hours post dose for both formulations. After C_{max}, leuprorelin concentrations declined in a similar fashion to comparable concentrations at 24 hours.

Discrepancies in the sampling time points between Eligard and LMIS were justified by the sampling points chosen in order to support the objectives of the clinical study, namely (1) To determine the safety and tolerability of LMIS 50 mg for up to 1 year of exposure following 2 subcutaneous doses given at 6 months apart in subjects with advanced prostate carcinoma; (2) To establish the efficacy of LMIS 50 mg for up to 1 year following 2 subcutaneous doses given at 6 months apart in subjects with advanced prostate carcinoma, as determined by the magnitude and duration of suppression of serum

testosterone levels; (3) To evaluate the pharmacokinetic behaviour of serum leuprorelin following 2 subcutaneous injections of LMIS 50 mg given 6 months apart.

A rise in leuprorelin LMIS at the end of study days 308-336 was apparent when compared to Eligard. This rise was coincident to a rise in testosterone levels as well as PSA levels. In order to fully characterize the pharmacodynamic effect of LMIS and provide bridging with Eligard, the applicant showed a graphical representation of the mean time-matched concentrations of leuprorelin and testosterone obtained from ADPC (Analysis Dataset of Pharmacokinetic Concentrations) of the main Phase 3 Study FP01C-13-001 and from Eligard 45 mg monograph. Concentrations of testosterone were then plotted against their time-matched leuprolide concentrations along with a linear regression (data not shown). The applicant provided a graphical representation in which both LMIS 50 mg and Eligard 45 mg appear to follow the same concentration-effect relationship. The approach was considered to adequately address the issues;

2.6.4. Conclusions on clinical pharmacology

Pharmacokinetics of leuprorelin has been investigated in one clinical study. The applicant has shown that the clinical study in the marketing authorisation documentation for EU- and US-Eligard is the same, allowing the bridging and making acceptable the use of Pre-clinical and clinical data of EU-Eligard as reference for Camcevi. Being the leuprorelin exposure, following LMIS 50 mg administration, lower than after Lupron 1 mg IV formulation safety can be bridged from Lupron 1 mg.

Bridging of efficacy is supported by the similarity between the PK profiles obtained with LMIS 50 mg and the literature-derived PK profiles obtained for Eligard 45 mg and other products. Similarity is further supported by a comparison of PD data (testosterone and PSA concentrations) between LMIS 50 mg and Eligard 45 mg.

The currently presented Clinical Pharmacology information is adequate to support the registration of Camcevi for the same indications as Eligard. The relevant sections of the SmPC are aligned with the reference product.

2.6.5. Clinical Efficacy

2.6.5.1. Dose response study(ies)

No dose-response studies were performed.

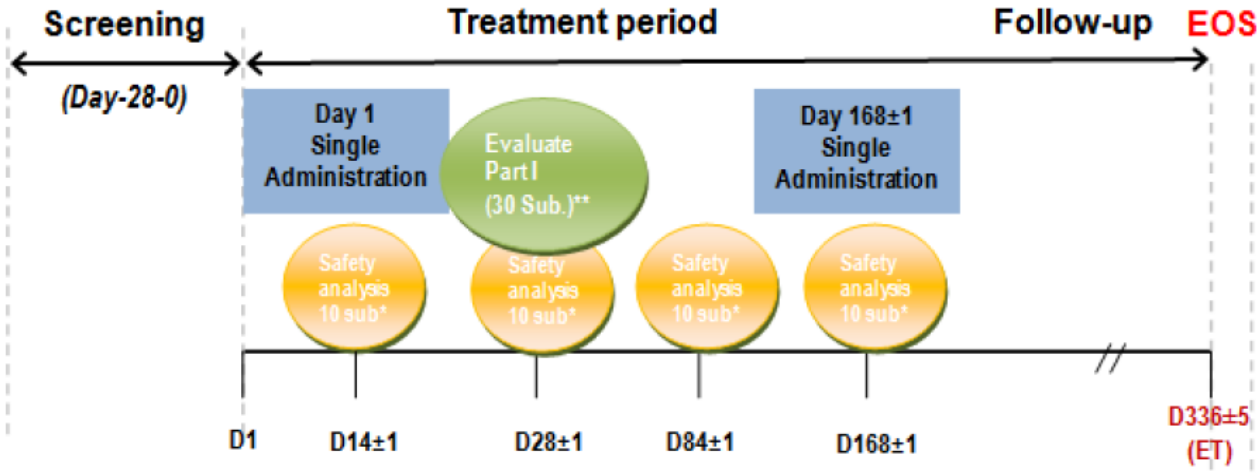
2.6.5.2. Main study(ies)

Title of study

Study FP01C-13-001

This is a completed pivotal Phase III, uncontrolled, multicentre, open-label, single-arm, 12-month, two-part PK, safety and PD/efficacy study conducted in 137 males with prostate carcinoma in need for androgen deprivation therapy (male adult subjects with histologically confirmed prostate carcinoma, baseline morning serum testosterone level > 150 ng/dL, Eastern Cooperative Oncology Group (ECOG) performance ≤ 2).

Figure 7. Study design and schedule for assessments (Study FP01C-13-001)



*The first 10 (of the 33) subjects served as a "sentinel" group for safety purposes and the IDMC conducted interim safety reviews for these subjects at the end of Week 2, Week 4 (Month 1), Week 12 (Month 3), and Week 24 (Month 6). These 4 interim safety reviews were performed in addition to the interim review of safety data, serum leuprorelin concentrations, and serum testosterone suppression status scheduled for the first 30 subjects following their Day 28 assessments in Part I.

** If ≥ 90% of Part I subjects (ie ≥ 27 of the 30 subjects) achieved suppression of serum testosterone to castrated levels within 4 weeks (approximately 1 month) of the initial dose and demonstrated acceptable safety and tolerability, then Part II study was opened and enrolled approximately 100 subjects.

Methods

This study was conducted in two parts.

Part I included the first 30 subjects, who had more frequent monitoring for safety. Once ≥90% of the 30 subjects achieved suppression of serum testosterone concentrations to castration levels (≤50 ng/dL) within 28 days of the initial dose, with acceptable safety and tolerability, Part II was opened, and the rest of the subjects were enrolled.

At the end of 24 weeks (Day 168), subjects in both Parts I and II who had tolerated LMIS 50 mg and shown castrate levels of serum testosterone concentrations (≤50 ng/dL) were dosed the second time with LMIS 50 mg, and were followed for tolerability, safety, efficacy, pharmacokinetics, and ancillary clinical and laboratory markers for an additional 24 weeks observation period.

Pharmacokinetic assessments of serum leuprorelin concentrations and pharmacodynamics assessments of serum testosterone concentrations using a validated LC/MS/MS method were performed. For subjects in Part I, serum samples were collected on Day 0 (prior to dosing, and hours 2, 4, 8 post-dosing), Days 1, 2, 3, 7, 14, 21, 28, 56, 84, 112, 140, 168 (Week 24: prior to dosing and hours 2, 4, 8 post-dosing), days 169, 170, 171, 196, 224, 252, 280, 308, and 336 (Week 48). Part II subjects had collection of blood samples at the same time points as above except that 2 and 8 hours post-dosing samples on Day 0 and Day 168 were not collected. For the PK/PD blood samples from Day 7 to Day 28, a ± 1 day window was allowed. From Week 8 (Day 56) to Week 20 (Day 140), a ± 3 day window was allowed. On Day 168 through Day 171, a ± 1 day window was allowed. From Day 196 through Day 308, a ± 3 day window was allowed. For the Day 336 visit, a ± 5 day window was allowed.

Study Participants

The study population consisted of 137 patients that were enrolled in the study. The applicant conducted this single multicentre Phase 3 Study FP01C-13-001 in the hospitals of Austria, Czech Republic, Germany, Lithuania, Poland, Slovakia, Taiwan, and the United States.

Inclusion criteria:

1. Males aged ≥18 years old.
2. Males with histologically confirmed carcinoma of the prostate.
3. Patients who were judged by the attending physician and/or principal investigator to be a candidate for ADT.
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:
    a. Absolute neutrophil count ≥1,500 cells/μL.
    b. Platelets ≥100,000 cells/μL.
    c. Haemoglobin ≥10 gm/dL.
    d. Total bilirubin ≤1.5 × upper limit of normal (ULN).
    e. Aspartate aminotransferase (AST) ≤ 2.5 × ULN.
    f. Alanine aminotransferase (ALT) ≤2.5 × ULN.
    g. Serum creatinine ≤1.5 mg/dL.
    h. Lipid profile within acceptable range according to investigator's opinion.
    i. Serum glucose within acceptable range according to investigator's opinion.
    j. HgbA1c within acceptable range according to investigator's opinion.
    k. Clinical chemistries (K, Na, Mg, Ca, and P) within acceptable range according to investigator's opinion.
    l. Urinalysis within normal range according to the investigator's opinion.
8. Agree to use male contraceptive methods during study trial.
9. In the investigator's opinion, the ability to understand the nature of the study and any hazards of participation, and to communicate satisfactorily with the Investigator and to participate in, and to comply with, the requirements of the entire protocol.
10. All aspects of the protocol explained and written informed consent obtained.

Exclusion criteria:

11. 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 was allowed during the study.
12. Receipt of any vaccination (including influenza) within 4 weeks of screening visit.
13. History of blood donation within 2 months of screening visit.

14. History of anaphylaxis to any luteinizing hormone releasing hormone (LH-RH) analogues.
15. Receipt of any LH-RH suppressive therapy within 6 months of screening visit.
16. Major surgery, including any prostatic surgery, within 4 weeks of screening visit.
17. History and concomitant clinical and radiographic evidence of central nervous system/spinal cord metastases. Patients at risk for spinal cord compression were excluded.
18. Clinical evidence of active urinary tract obstruction and patients at risk for urinary obstruction.
19. History of bilateral orchiectomy, adrenalectomy, or hypophysectomy.
20. History or presence of hypogonadism, or receipt of exogenous testosterone supplementation within 6 months of screening visit.
21. Clinically significant abnormal electrocardiogram (ECG) and/or history of clinically significant cardiovascular disease as judged by the investigator.
22. History of drug and/or alcohol abuse within 6 months of screening visit.
23. Contraindication to leuprorelin or an LH-RH agonist as indicated on package labelling.
24. Use of 5-alpha reductase inhibitor within the last 6 months of screening visit.
25. History or presence of insulin-dependent diabetes mellitus (Type I). Presence of well controlled diabetes mellitus Type II was allowed if only oral hypoglycaemic was required.
26. Use of systemic corticosteroids at a dose > 10 mg/d or anti-androgens.
27. Use of any investigational agent within 4 weeks of Screening Visit.
28. Use of any over-the-counter (OTC) medication within 4 weeks of screening visit except for those listed in the permitted concomitant treatment section.
29. Uncontrolled intercurrent illness that would jeopardize the patient's safety, interfere with the objectives of the protocol, or limit the patient's compliance with study requirements, as determined by the Investigator in consultation with the sponsor.

Radiotherapy as part of a multimodality assessment was not explored (see exclusion criterion 11 above).

Treatments

Camcevi is administer as a single subcutaneous injection of LMIS 50 mg every 24 weeks (approximately 6 months; over the course of 2 doses on Day 1 and Day 168). Two segments were conducted.

In Part I, approximately 30 patients were enrolled, dosed once with LMIS 50 mg, and observed for at least 4 weeks (approximately 1 month, Day 28). The first 10 (of the 30) patients served as a "sentinel" group for safety purposes in which more frequent monitoring of safety endpoints and serum testosterone concentrations were scheduled. These interim safety analyses were performed by the independent data monitoring committee (IDMC) for the first 10 patients at the end of Week 2, Week 4 (approximately 1 month), Week 12 (approximately 3 months), and Week 24 (approximately 6 month).

Patients enrolled in Part I also had another interim evaluation of safety. During this safety evaluation, enrolment was suspended until the safety evaluation had been completed. If $\geq$ 90% of Part I patients ($\geq$ 27 out of 33 patients) were to achieve suppression of serum testosterone to castrate levels ($\leq$ 50 ng/dL) within 4 weeks (approximately 1 month; by Day 28) of the initial dose and the LMIS 50 mg was found to be tolerable and safe, Part II would begin and therefore the remaining patients were enrolled.

At the end of Week 24 (approximately 6 months, Day 168), patients in both Parts I and II who

tolerated LMIS 50 mg and showed a castrate serum testosterone level were dosed the second time with LMIS 50 mg. After the second administration of LMIS 50 mg by SC injection, patients were followed for safety, tolerability, efficacy, pharmacokinetics, and ancillary clinical and laboratory markers for an additional 24 weeks.

Objectives

The primary objectives:

- To determine the safety and tolerability of LMIS 50 mg for up to one year of exposure following two subcutaneous doses given at 24 weeks (approximately 6 months) apart in patients with advanced prostate carcinoma;
- To establish the efficacy of LMIS 50 mg for up to one year following two subcutaneous doses given at six months apart in patients with advanced prostate carcinoma, as determined by the magnitude and duration of suppression of serum testosterone levels;
- To evaluate the pharmacokinetic behaviour of serum leuprorelin following two subcutaneous injections of LMIS 50 mg given approximately six months apart.

The secondary objective:

- To characterize the effects of LMIS 50 mg on the ancillary laboratory markers of serum PSA and LH.

Outcomes/endpoints

- **Primary endpoints:**To determine the safety and tolerability of LMIS 50 mg by: symptoms (by AUA Symptom Score qsheet, complete blood count with platelets, clinical chemistries (K, Na, Mg, Ca and P), urinalysis, serum glucose, lipid profile (LDL, HDL, triglycerides) and HgbA1c lead resting electrocardiograms (ECGs) per the Investigator's judgment.
- To determine the percentage of subjects with a serum testosterone concentration suppressed to castrate levels (≤ 50 ng/dL) by Day 28 ± 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).
- To determine the pharmacokinetic behavior of leuprorelin by full pharmacokinetic profiles from serum leuprorelin concentrations in Part I subjects will be performed. Additional serum leuprorelin concentration data will be collected during Part II. The pharmacokinetic behavior of leuprorelin will be determined on a more limited basis for subjects in Part II.

Secondary endpoints:

- 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" phenomenon (*i.e.*, related to the second dose of LMIS 50 mg).
- Effect of LMIS 50 mg on serum PSA levels.
- Effect of LMIS 50 mg on serum LH levels.

Sample size

A sample size of 120 patients was estimated to achieve the 85% power to detect a difference of 0.0700 using a one-sided binomial test. A pre-specified interim analysis of efficacy was performed after 100 patients had completed the Day 28 assessment and a sample size reassessment was carried out to determine whether additional patients needed to be enrolled. The estimated conditional power was 99.07%. Thus, the trial continued as planned with the current sample size. A total of 137 patients were enrolled in the study at the end. If ≥ 90% of Part I subjects (ie ≥ 27 of the 30 subjects) achieved suppression of serum testosterone to castrated levels within 4 weeks (approximately 1 month) of the initial dose and demonstrated acceptable safety and tolerability, then Part II study was opened and enrolled approximately 100 subjects

Randomisation and Blinding (masking)

This was an open-label, single arm study and therefore no blinding procedure was performed.

Statistical method

Analysis populations:

Three populations were analysed in this study: ITT, PP, and safety populations.

- The ITT population was defined as any subject who received at least one dose of LMIS 50 mg.
- The PP population was defined as subjects who received 2 doses of LMIS 50 mg and met the inclusion/exclusion requirements of the protocol without major protocol deviations.
- The safety population was defined as any subject who received a dose of LMIS 50 mg.

All 137 subjects were included in the ITT and safety populations. Thirteen subjects were excluded from the PP population due to major protocol deviations or because they did not receive the second dose of LMIS 50 mg, leaving 124 subjects in the PP population for the efficacy analysis.

Description of statistical methods:

1. The ITT (N=137) and PP (N=124) populations were used in the efficacy analyses. Any subject receiving a dose of LMIS 50 mg was included in the safety analysis.
2. For descriptive statistics, continuous variables were presented as number of observations, mean, standard deviation, median, range, Hodges-Lehmann estimator and 95% CI. Categorical variables were presented by frequency and percentage. Changes from baseline were tested by a paired *t*-test or Wilcoxon signed-rank test for continuous variables using a significance level of 0.05.
3. For efficacy endpoints, the percentage of subjects with a serum testosterone of ≤ 50 ng/dL (castrate level) by Day 28 ± 1(day) was analysed using a standard large sample approximation to a Binomial distribution. The percentage of subjects with testosterone suppression (≤ 50 ng/dL) from Day 28 through Day 336 was analysed using a Kaplan-Meier approach. The duration of time to an event was summarised by Kaplan-Meier plot, and presented as event number, percentage, 95% confidence interval for percentage, mean, median and 95% confidence interval for median. The subjects exhibiting post-suppression excursions of serum testosterone to > 50 ng/dL, either through "breakthrough", or through the "acute-on-chronic" excursions, were presented as a count, percentage and 95% CI. The serum PSA levels and serum LH levels during the study were summarised by descriptive statistics, and the change

from baseline was summarised descriptively and a paired t-test or Wilcoxon signed-rank test was used with significance level of 0.05.

4. For safety endpoints, change of continuous variables including bone and urinary pain measurement (by VAS scale), urinary signs and symptoms (by AUA Symptom Score sheet), vital signs and lab data were summarised descriptively and a paired t-test or Wilcoxon signed-rank test was used at a significance level of 0.05. The transition matrix for categorical variables was presented.
5. Adverse events were coded with MedDRA and a summary frequency table of adverse events was provided. The severity and relationship to study medication of adverse events were summarised as well. Furthermore, if any serious adverse events occurred, the brief summary about serious adverse events was described and listed in tables.
6. For pharmacokinetic parameters, arithmetic means, standard deviations and coefficients of variation were calculated.

Sensitivity analyses:

The analyses for the efficacy endpoints were performed in the ITT population and the PP population. The sensitivity analyses for the duration of serum testosterone levels ≤50 ng/dL were performed, in which patients missing testosterone level at any visit were censored for the analysis of duration time of subject with a serum testosterone of ≤50 ng/dL from Day 28 through Day 336. Subjects were censored at the last testosterone measurement before the first missing visit if no prior escape occurred; otherwise, subjects were considered to have an event at the escape visit. If a subject maintained suppression from Day 28 through Day 336 and completed the study without missing any testosterone tests, the subject was censored at the EOS visit.

The sensitivity analysis was performed for the primary efficacy endpoint to determine whether censoring for any missing data would affect the analysis of duration time of subject with a serum testosterone of ≤50 ng/dL from Day 28 through Day 336. The subject was censored at the last testosterone measurement before the first missing visit if no prior escape occurred. The subject was considered having event at the escape visit otherwise. If a subject maintained suppression from Day 28 through Day 336 and completed the study without missing any testosterone tests, the subject was censored at the EOS visit. Additionally, given that the missing testosterone value might have not been missing at random (MAR), a sensitivity analysis of duration time of subject with a serum testosterone levels of ≤50 ng/dL from Day 28 through Day 336 was performed for the subset of subjects who completed the study and did not have any testosterone data missing beyond visit Day 28 through visit Day 336.

The analysis with censoring for any missing data was performed for patients in the ITT as well as the PP population.

Post hoc analyses:

The post hoc analysis was performed in the subjects with elevated PSA at baseline.

Handling of dropouts and missing data:

For missing data related to a safety or efficacy endpoints, no method of imputation was applied. For the primary efficacy endpoint, the drop-out and missing values were handled by the censoring rules suggested by the FDA, see Table 4

Table 4. Censoring rules (Study FP01C-13-001)

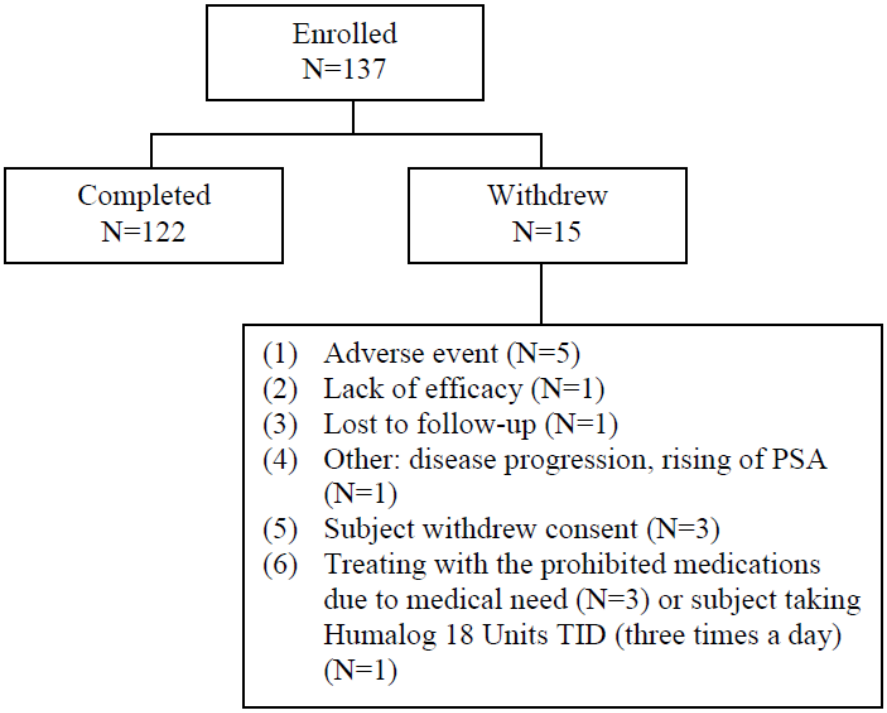
Suppression by Day 28			To Be Handled As
Subject Discontinued	Day 28-336 or Day of Discontinuation		
	More Than 1 Missing Testosterone Value	Any Escape	
Yes	No	No	Censored on day of last measurement prior to discontinuation
Yes	No	Yes	Event on day of first escape
Yes	Yes	No	Censored on day of last measurement before the first missing
Yes	Yes	Yes	Event on day of first escape
No	No	No	Censored on EOS visit
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

Escape was defined as a serum testosterone level greater than 50 ng/dL from Day 28 (V9) to Day 336 (V23/EOS). The data of subjects with suppressions on Day 28 visit were handled based on the above censoring rules and the data of subjects without suppression on Day 28 visit or subjects with missing testosterone value on Day 28 visit were analysed as events on Day 28.

Results

Participant flow

Figure 8. Disposition of the patients (Study FP01C-13-001)



N: number of subject

Recruitment

A maximum of 133 subjects were anticipated to be enrolled into this study. A total of 137 subjects were enrolled in the study.

- First subject was enrolled 12-Aug-2014.
- Last subject completed last visit 02-Sep-2016.

Of the 137 enrolled subjects, 15 (10.9%) subjects did not complete the study.

Conduct of the study

The study protocol was amended four times. The original protocol was dated 24-Mar-2014 and the latest version 1.4 was dated 14-Oct-2015. The applicant submitted the protocol versions and descriptions of the protocol amendments. The amendments concerned various sections including efficacy, safety, pharmacokinetics and statistical analyses. The applicant stated, that no changes were made in the conduct of the study or planned analyses and the study was performed in accordance of the study protocol FP01C-13-001 version 1.4, dated October 14, 2015.

Protocol deviations

All together 452 protocol deviations were reported, of which 14 incidences in eleven patients were reported as major deviations. The major deviations comprised improper storage of four IP packages, but these were not used in patients. Major deviations occurring in patients included SAEs not reported (2), incorrect kit of IP (2), patient not attending visits (2), unacceptable medications used (4), PK-samples not conducted properly (2) and serum creatinine increase (1). Thirteen subjects were

excluded from the PP population due to major protocol deviations or because they did not receive the second dose of LMIS 50 mg.

Baseline data

The demographics and baseline characteristics of all 137 enrolled subjects (ITT population) were summarised based on age, gender, ethnicity, race, tumor history (years of diagnosis, T [primary tumor], N [spread to lymph node], M [metastatic stage of tumor]), and ECOG performance status. The summary of demographics is presented in Table 5.

Table 5. Summary of demographics (ITT population, Study FP01C-13-001)

Variable / Status	Part I (N=33)	Part II (N=104)	Total (N=137)
Age (years)*[1]			
n	33	104	137
mean (SD)	73.5 (8.40)	70.3 (8.70)	71.1 (8.70)
median (min, max)	74.0 (54, 86)	70.0 (51, 88)	71.0 (51, 88)
Hodges-Lehmann estimator	74.0	70.5	71.0
95% CI	(70.5, 76.5)	(68.6, 72.0)	(69.6, 72.5)
Gender			
Male	33 (100.0%)	104 (100.0%)	137 (100.0%)
Ethnicity			
Hispanic	2 (6.1%)	1 (1.0%)	3 (2.2%)
Non - Hispanic	30 (90.9%)	31 (29.8%)	61 (44.5%)
Unknown	1 (3.0%)	72 (69.2%)	73 (53.3%)
Race			
Asian	4 (12.1%)	1 (1.0%)	5 (3.6%)
Black	4 (12.1%)	4 (3.8%)	8 (5.8%)
Unknown	0 (0.0%)	1 (1.0%)	1 (0.7%)
White	25 (75.8%)	98 (94.2%)	123 (89.8%)
Diagnosis (years)*[2]			
n	33	104	137
mean (SD)	8.0 (7.19)	3.9 (6.08)	4.9 (6.58)
median (min, max)	6.0 (0, 25)	0.0 (0, 36)	2.0 (0, 36)
Hodges-Lehmann estimator	7.5	3.0	4.0
95% CI	(5.4, 10.6)	(2.7, 5.1)	(3.8, 6.0)
Diagnosis (days)*[2]			
n	33	104	137
mean (SD)	2922.5 (2597.57)	1446.5 (2220.67)	1802.1 (2392.41)
median (min, max)	2254.0 (12, 9066)	158.5 (0, 13290)	633.0 (0, 13290)
Hodges-Lehmann estimator	2750.0	1100.8	1443.5
95% CI	(2001.4, 3843.5)	(1014.7, 1878.4)	(1397.8, 2206.3)
Staging*[4]			
I	1 (3.0%)	3 (2.9%)	4 (2.9%)
II	8 (24.2%)	23 (22.1%)	31 (22.6%)
III	5 (15.2%)	32 (30.8%)	37 (27.0%)
IV	9 (27.3%)	23 (22.1%)	32 (23.4%)
NO PATH REPORT AVAILABLE	1 (3.0%)	0 (0.0%)	1 (0.7%)
UNK	9 (27.3%)	23 (22.1%)	32 (23.4%)
ECOG performance status			
0	30 (90.9%)	84 (80.8%)	114 (83.2%)
1	3 (9.1%)	19 (18.3%)	22 (16.1%)
2	0 (0.0%)	1 (1.0%)	1 (0.7%)

[1]Age was calculated as (Date of informed consent - Date of birth)/365.25 and round down to integer.
[2]Diagnosis of prostate carcinoma history (years) was calculated as (Date of informed consent - Date of diagnosis)/365.25 and round down to integer; and diagnosis of prostate carcinoma history (days) was calculated as (Date of informed consent - Date of diagnosis). Subject TW12-001's date of diagnosis is the same as date of informed consent.
[3]TNM of prostate carcinoma history.

[4]Staging of prostate carcinoma history.

Concomitant treatments allowed during the study:

- Bisphosphonates.
- Denosumab.
- Supplementation of vitamin D and calcium.
- Plain, over-the-counter multi-vitamins.
- Glucocorticosteroids were allowed if being used as a replacement therapy.
- Pain medications.
- Oral hypoglycemic medicines.
- Radiation for pain control.

Treatment compliance:

All subjects were administered LMIS 50 mg via subcutaneous injection at the study site. Of 137 subjects enrolled in the study, 128 subjects received both doses of LMIS 50 mg. The compliance was 93.4%.

Numbers analysed

Three populations were analysed in this study: ITT, PP, and safety populations. The ITT population was defined as any subject who received at least one dose of LMIS 50 mg. The PP population was defined as subjects who received 2 doses of LMIS 50 mg and met the inclusion/exclusion requirements of the protocol without major protocol deviations. The safety population was defined as any subject who received a dose of LMIS 50 mg. All 137 subjects were included in the ITT and safety populations. Table 6.

Table 6. Summary of study population (enrolled subjects, Study FP01C-13-001)

Variable / Status	Part I (N=33)	Part II (N=104)	Total (N=137)
ITT population			
Included	33 (100.0%)	104 (100.0%)	137 (100.0%)
PP population			
Excluded	6 (18.2%)	7 (6.7%)	13 (9.5%)
Included	27 (81.8%)	97 (93.3%)	124 (90.5%)
Safety population			
Included	33 (100.0%)	104 (100.0%)	137 (100.0%)
Subject has major protocol deviation			
No	29 (87.9%)	97 (93.3%)	126 (92.0%)
Yes	4 (12.1%)	7 (6.7%)	11 (8.0%)

Outcomes and estimation

Primary efficacy endpoint:

The percentage of subjects with a serum testosterone of ≤ 50 ng/dL (castrate level) by Day 28 was 98.5% (135/137 subjects) in the ITT population and 99.2% (123/124 subjects) in the PP population, see Table 7. Two subjects did not reach the castrated level of mean serum testosterone by Day 28 (V9).

Table 7. Summary of subjects with a serum testosterone of ≤ 50 ng/dL by 28 Days (ITT and PP populations, Study FP01C-13-001)

	ITT Population (N=137)		PP Population (N=124)	
Variable / Status	Summary	95% CI	Summary	95% CI
Day 28 (V9)				
n	137		124	
Yes	135 (98.5%)	(94.8, 99.8)	123 (99.2%)	(95.6, 100.0)
No	2 (1.5%)		1 (0.8%)	

Most subjects had a serum testosterone of ≤50 ng/dL from Day 28 through Day 336, except for four subjects. Two subjects escaped on Day 28 (V9), one subject escaped on Day 169 (V15) and the other subject escaped on Day 170 (V16). No unexpected findings based on these patient narratives were found. The remaining subjects had a serum testosterone of ≤50 ng/dL from Day 28 through Day 336.

The percentage of subjects with castrate level testosterone from Day 28 through Day 336 was analysed using the Kaplan-Meier approach, in which an event was defined as occurring in subjects with a serum testosterone level > 50 ng/dL at or before Day 336. The percentage of subjects with testosterone suppression during this period was 97.0% (133/137 subjects) in the ITT population and 97.6% (121/124 subjects) in the PP population, see Table 8.

Table 8. Summary of subjects with a serum testosterone of ≤ 50 ng/dL from Day 28 through Day 336 (IIT and PP Populations, Study FP01C-13-001)

	ITT Population (N=137)	PP Population (N=124)
Variable / Status	Summary	Summary
Subjects with testosterone suppression (<=50 ng/dL) from Day 28 through Day 336*[1]		
total number	137	124
event number (%)	4 (2.9%)	3 (2.4%)
mean time (Days)	140.9	141.8
median time (Days)	-	-
95% CI of median (Days)	-	-
suppression rate*[2] by Day 336 (95% CI)	97.0 (92.2, 98.9)	97.6 (92.7, 99.2)
95% RCI by Day 336*[3]	(92.5, 99.4)	

*[1] The Kaplan-Meier method was used to analyze the duration of subject with testosterone suppression from Day 28 through Day 336. Event was defined as subjects had testosterone to >50 ng/dL.
*[2] The suppression rate of subjects with testosterone suppression (<=50 ng/dL) by Day 336 was provided.
*[3] The 95% RCI by Day 336 was provided by ADDPLAN software and manually scribed to the SAS generated table.

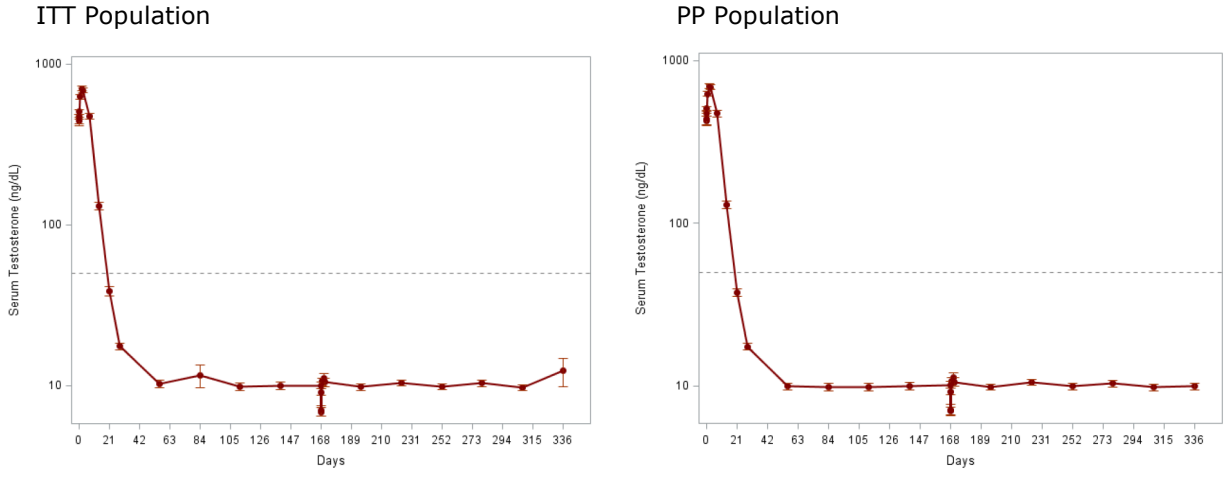
At 7–8 weeks after the first injection, the mean serum testosterone level reached a plateau of approximately 10 ng/dL. Serum testosterone remained at this level until the end of the study at Week 48 (Day 336). Transient increase in mean serum testosterone levels occurred within 24 to 72 hours following the administration of the second dose of LMIS 50 mg ("acute-on-chronic" phenomenon). This transient increase in serum testosterone level was back to the castration levels by Day 196 (V18), and remained below the castration levels until the end of study (Day 336/V23). The primary endpoint results are shown in Table 9 and Figure 9. Serum testosterone levels over time (Study FP01C-13-001).

Table 9. Primary endpoint results for main Study FP01C-13-001

Population	**# Enrolled/ completed**	**Percentage of patients with serum testosterone ≤ 50 ng/dL (95% CI)**	
		By Day 28	**Day 28–Day 336**
ITT[a]	137/137	98.5 (94.8–99.8)	97.0 (92.2–98.9)
PP[b]	137/124	99.2 (95.6–100.0)	97.6 (92.7–99.2)

[a]Any patient who received at least 1 dose of LMIS 50 mg
[b]Any patient who received 2 doses of LMIS 50 mg, met the inclusion/exclusion criteria of the protocol, and had no major protocol violation
CI = confidence interval; ITT = intent-to-treat; LH = luteinising hormone; LMIS = leuprorelin mesilate injectable suspension; PP = per protocol

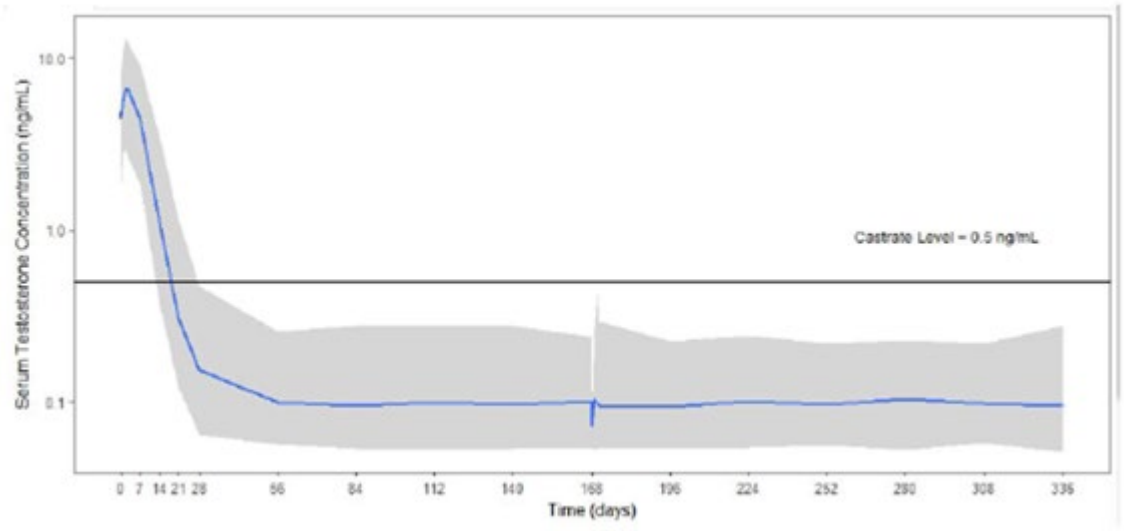
Figure 9. Serum testosterone levels over time (Study FP01C-13-001)



ITT = intent-to-treat; PP = per protocol

The administration of LMIS 50 mg achieved the therapeutic goal of suppressing the serum testosterone to castrated level in 98% subjects on Day 28 and the suppression rate was maintained at 97% at the end of this study.

Figure 10. Median (95% prediction interval) serum testostetrone concentration vs. time after a single sc dose of LMIS 50 mg (Day 0) or multiple SC dose of LMIS 50 mg (Day 168), semi log scale



Sensitivity analysis:

The sensitivity analyses showed that the suppression rate for sensitivity analysis was 97.0% (95% CI: 92.2-98.9) for the ITT population, 97.6% (95% CI: 92.7- 99.2) for the PP population, and 97.4% (95% CI: 92.3-99.2) for completed cases. All lower 95% confidence interval bounds for the suppression rate were greater than 90%. Refer to Table 9

Table 10. Summary of sensitivity analysis for patients with testosterone suppression ≤ 50 ng/dL from Day 28 through Day 336 (IIT, PP populations and completed cases, Study FP01C-13-001).

	ITT Population (N=137)	PP Population (N=124)	Completed Cases (N=117)
Variable / Status	**Summary**	**Summary**	**Summary**
Subjects with testosterone suppression (<=50 ng/dL) from Day 28 through Day 336*			
total number	137	124	117
event number (%)	4 (2.9%)	3 (2.4%)	3 (2.6%)
mean time (Days)	140.9	141.8	141.7
median time (Days)	-	-	-
95% CI of median (Days)	-	-	-
suppression rate** by Day 336 (95% CI)	97.0 (92.2, 98.9)	97.6 (92.7, 99.2)	97.4 (92.3, 99.2)

*The Kaplan-Meier method was used to analyze the duration of subject with testosterone suppression from Day 28 through Day 336. Event was defined as subjects had testosterone to >50 ng/dL.
**The suppression rate of subjects with testosterone suppression (<=50 ng/dL) by Day 336 was provided.

Secondary endpoints:

The proportion of subjects exhibiting post-suppression excursions of serum testosterone to > 50 ng/dL

The number of subjects who returned at each visit depended on whether there was missing serum testosterone value at the scheduled visit.

One subject dropped out before Day 56 (V10). Two subjects) did not reach castration on Day 28 (V9).

In the ITT population (137 subjects), there were 134 subjects eligible for this endpoint analysis on Day 56 (V10). The total number of subjects who reached castration on Day 28 and had non-missing serum testosterone values at scheduled visits taken was 100%.

Two subjects exhibited post-suppression elevated castrate levels of testosterone (> 50 ng/dL) during the study. Both were due to the acute-on-chronic surge following the second administration of LMIS 50 mg. One subject in both the ITT and PP populations was observed with mean serum testosterone level > 50 ng/dL on Day 169 (V15). His serum testosterone was 53.9 ng/dL on Day 169 (V15), 61.4 ng/dL on Day 170 (V16), and 59.7 ng/dL on Day 171 (V17). His serum testosterone level was below the castrated level (13.2 ng/dL) on V18 (Day 196). The other subject in both the ITT and PP populations exhibited post-suppression excursion on Day 170 (V16) with serum testosterone level 54.7 ng/dL. His serum testosterone level was 30.4 ng/dL on Day 171 (V17). All the above excursions of serum testosterone occurred after administering the second dose of LMIS 50 mg, which may be attributed to the mild surge effect of LH. The percentage of subjects exhibiting post-suppression elevation of serum testosterone was 0% in both ITT and PP populations at the end of the study (Day 336). Based on more detailed data provided during the procedure, only very slight and transient testosterone level breakthroughs were observed in these two patients and also the LH levels were suppressed. The elevations of testosterone levels following the second dose of LMIS 50 mg were concluded to be related to the acute-on-chronic excursion of LH.

The efficacy of two separate doses of LMIS 50 mg was further analysed by examining the percentage of subjects with the serum testosterone less than 20 ng/dL on Day 28 and Day 336.

The percentage of subjects with a serum testosterone level ≤ 50 ng/dL (castrate level) by Day 28 was 98.5% (135/137) in the ITT population. Of 135 subjects who achieved the castrated level serum testosterone (≤ 50 ng/dL), 95 subjects (95/135, 70.4%) achieved serum testosterone level < 20 ng/dL on Day 28.

On Day 336, all subjects who completed the study (122/122) achieved castrated serum testosterone level (≤ 50 ng/dL), among which 117 subjects (117/122, 95.9%) achieved serum testosterone level < 20 ng/dL using the more stringent criteria.

The first dose of LMIS 50 mg reduced the serum testosterone to lower than the castrate level (< 20 ng/dL) in 70% subjects on Day 28. The suppressed serum testosterone level (< 20 ng/dL) was maintained to the end of study (Day 336) after the second injection of LMIS 50 mg on Day 168 in more than 95% subjects who completed the study.

Effect of LMIS 50 mg on serum PSA levels

The administration of LMIS 50 mg reduced the serum PSA levels after the first injection, and the effect remained until the end of the study in majority of the patients. The applicant reported a mild rebound in PSA levels, which was observed from Day 252 to Day 336 (V23/EOS). Refer to Table 11, Table 12 and Figure 11.

Table 11. Summary of PSA levels and change from baseline (ITT and PP Population, Study FP01C-13-001)

	ITT Population (N=137)			PP Population (N=124)		
Variable / Status	Summary	Change	P-value*	Summary	Change	P-value*
Day 0 (V2)						
n	137			124		
mean (SD)	84.747 (382.4744)			70.240 (333.4071)		
Median (min, max)	8.310 (0.06, 2748.44)			8.245 (0.06, 2748.44)		
Hodges-Lehmann estimator	12.065			11.033		
95% CI	(20.127, 149.368)			(10.974, 129.506)		
Day 28 (V9)						
n	137	137	<0.001	124	124	<0.001
mean (SD)	21.709 (80.9601)	-63.039 (304.0044)		18.040 (64.3671)	-52.200 (271.1626)	
median (min, max)	3.260 (0.06, 635.79)	-4.600 (-2290.86, 22.72)		3.215 (0.06, 525.91)	-4.550 (-2290.86, 22.72)	
Hodges-Lehmann estimator	4.090	-6.335		3.815	-6.050	
95% CI	(8.030, 35.387)	(-114.401, -11.676)		(6.598, 29.481)	(-100.402, -3.999)	
Day 84 (V11)						
n	136	136	<0.001	124	124	<0.001
mean (SD)	5.017 (18.4060)	-80.283 (369.8575)		3.575 (9.7538)	-66.665 (326.5933)	
Median (min, max)	0.655 (0.06, 185.86)	-6.960 (-2714.06, 1.84)		0.570 (0.06, 75.86)	-6.960 (-2714.06, 1.84)	
Hodges-Lehmann estimator	0.960	-9.855		0.870	-9.470	
95% CI	(1.896, 8.139)	(-143.005, -17.560)		(1.841, 5.309)	(-124.720, -8.610)	

Day 168 (V14)						
n	129	129	<0.001	124	124	<0.001
mean (SD)	2.577 (7.5404)	-66.648 (321.6754)		2.641 (7.6833)	-67.599 (327.8818)	
Median (min, max)	0.340 (0.06, 56.56)	-7.510 (-2691.88, 2.21)		0.325 (0.06, 56.56)	-7.355 (-2691.88, 2.21)	
Hodges-Lehmann estimator	0.630	-9.925		0.605	-9.768	
95% CI	(1.264, 3.891)	(-122.688, -10.608)		(1.275, 4.006)	(-125.883, -9.315)	
Day 252 (V20)						
n	124	124	<0.001	121	121	<0.001
mean (SD)	3.545 (13.0604)	-66.880 (327.7307)		3.620 (13.2136)	-68.118 (331.6975)	
Median (min, max)	0.255 (0.06, 117.54)	-7.005 (-2688.04, 44.89)		0.240 (0.06, 117.54)	-6.900 (-2688.04, 44.89)	
Hodges-Lehmann estimator	0.550	-9.650		0.565	-9.605	
95% CI	(1.223, 5.866)	(-125.137, -8.623)		(1.242, 5.999)	(-127.822, -8.415)	
Day 336 (V23/EOS)						
n	131	131	<0.001	122	122	<0.001
mean (SD)	12.837 (65.5957)	-75.314 (351.0376)		7.972 (37.1654)	-63.317 (321.7382)	
Median (min, max)	0.230 (0.06, 633.57)	-7.120 (-2550.65, 245.40)		0.215 (0.06, 318.05)	-7.160 (-2550.65, 245.40)	
Hodges-Lehmann estimator	0.708	-9.513		0.675	-9.250	
95% CI	(1.498, 24.175)	(-135.991, -14.636)		(1.311, 14.634)	(-120.985, -5.648)	

The PSA was analyzed as unit ng/mL.
*Paired T test or Wilcoxon signed rank test would be used to test the change from baseline for continuous variables.

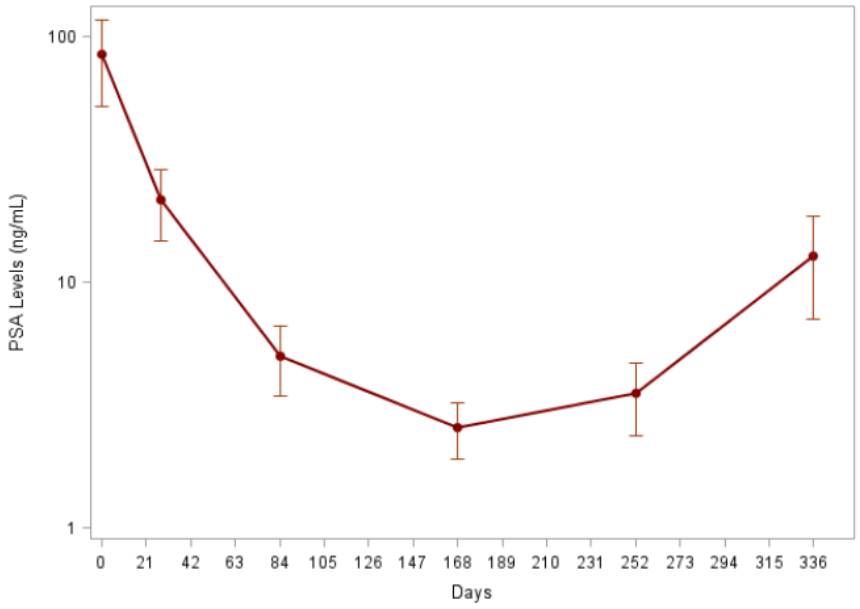
Table 12. Prostate-specific antigen levels over time (Study FP01C-13-001)

	Serum PSA levels (ng/mL), Mean ± SD					
	Baseline	**Day 28**	**Day 84**	**Day 168**	**Day 252**	**Day 336**
ITT[a]	84.747± 382.4744	21.709± 80.9601[#]	5.017± 18.4060[#]	2.577± 7.5404[#]	3.545± 13.0604[#]	12.837± 65.5957[#]
PP[b]	70.240± 333.4071	18.040± 64.3671[#]	3.575± 9.7538[#]	2.641± 7.6833[#]	3.620± 13.2136[#]	7.972± 37.1654[#]

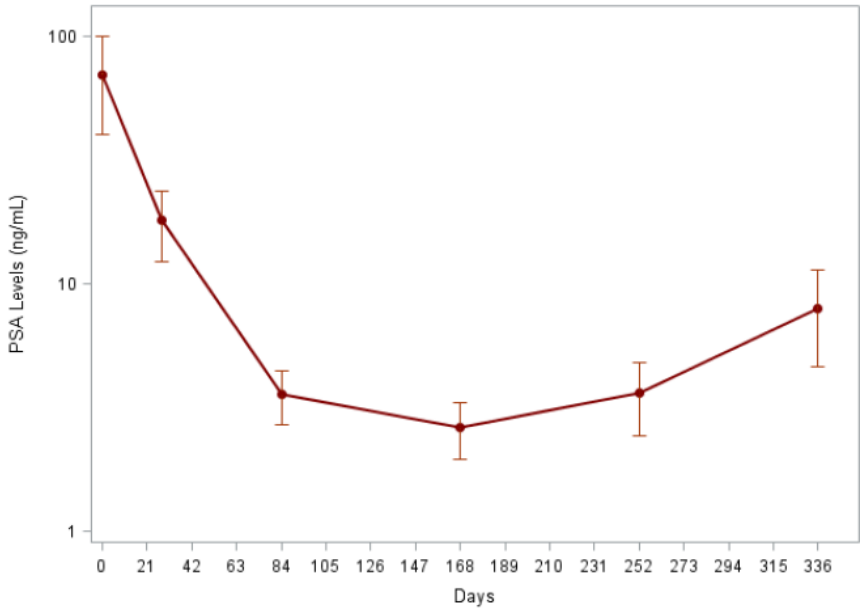
[a]Any patient who received at least 1 dose of LMIS 50 mg
[b]Any patient who received 2 doses of LMIS 50 mg, met the inclusion/exclusion criteria of the protocol, and had no major protocol violation
[#]$p < 0.001$
ITT = intent-to-treat; PP = per protocol; PSA = prostate-specific antigen; SD = standard deviation.

Figure 11. PSA levels over time (ITT and PP population, Study FP01C-13-001)

ITT



PP



Post hoc -analysis

Table 13. Summary of PSA for patients with elevated PSA at baseline (ITT Population, Study FP01C-13-001)

	ITT Population (N=99)							
Visit	n	Decrease <50%	Decrease 50 to <90%	Decrease 90 to <95%	Decrease ≥95%	Increase	≤4 ng/mL	>4 ng/mL
Day 28 (V9)	99	26 (26.3%)	65 (65.7%)	4 (4.0%)	1 (1.0%)	3 (3.0%)	47 (47.5%)	52 (52.5%)
Day 84 (V11)	98	4 (4.1%)	31 (31.6%)	22 (22.4%)	41 (41.8%)	0 (0.0%)	75 (76.5%)	23 (23.5%)
Day 168 (V14)	94	2 (2.1%)	24 (25.5%)	11 (11.7%)	57 (60.6%)	0 (0.0%)	80 (85.1%)	14 (14.9%)
Day 252 (V20)	90	2 (2.2%)	16 (17.8%)	13 (14.4%)	58 (64.4%)	1 (1.1%)	76 (84.4%)	14 (15.6%)
Day 336 (V23)	88	4 (4.5%)	17 (19.3%)	11 (12.5%)	55 (62.5%)	1 (1.1%)	76 (86.4%)	12 (13.6%)

Six subjects did not have PSA values available at the end of study. Three PC patients did not receive the 2nd dose of LMIS 50 mg for the following reasons: death in one patient, consent withdrawal and refusal to return for the early-termination visit in one patient, and withdrawal due to serious adverse event occurrence before receiving the 2nd dose of LMIS 50 mg in one patient. The other 3 patients received the 2nd dose of LMIS 50 mg but did not have the PSA level measurement for the following reasons: death in two PC patients and loss to follow up in one patient after V20. The patient characteristics and laboratory values of patients without PSA at the end of study did not show any unexpected findings.

Effect of LMIS 50 mg on serum LH levels

Serum LH levels were determined in two different laboratories to exclude the possibility that data variation resulted from different laboratory procedures. The administration of LMIS 50 mg reduced the serum LH levels after the first injection, and the effect remained until the end of the study. An acute and transient increase of mean serum LH levels was observed after each administration of the LMIS 50 mg and a slight increase in mean LH level was observed at the end of study on Day 336. Refer to Table 14 and Table 15, and Figure 12 and Figure 13

Table 14. Summary of LH levels and change from baseline by BA lab (ITT and PP populations Study FP01C-13-001)

	ITT Population (N=137)			PP Population (N=124)		
Variable / Status	Summary	Change	P-value*	Summary	Change	P-value*
Day 0 (V2) - Prior Dosing						
n	137			124		
mean (SD)	5.125 (3.0421)			5.016 (2.9666)		
median (min, max)	4.320 (1.54, 16.20)			4.215 (1.54, 16.20)		
Hodges-Lehmann estimator	4.645			4.555		
95% CI	(4.611, 5.639)			(4.489, 5.543)		
Day 28 (V9)						
n	137	137	<0.001	124	124	<0.001
mean (SD)	0.57327 (1.369448)	-4.55214 (2.846677)		0.45587 (0.460792)	-4.56026 (2.762261)	
median (min, max)	0.35000 (0.0575, 15.6000)	-3.88100 (-14.9000, 3.3000)		0.31950 (0.0575, 3.3600)	-3.74850 (-14.9000, -1.4280)	
Hodges-Lehmann estimator	0.38250	-4.14850		0.36900	-4.13200	
95% CI	(0.34189, 0.80464)	(-5.03309, -4.07118)		(0.37396, 0.53778)	(-5.05128, -4.06925)	
Day 168 (V14)						
n	129	129	<0.001	124	124	<0.001
mean (SD)	0.10699 (0.251897)	-4.99131 (3.051810)		0.10891 (0.256751)	-4.90722 (2.972342)	
median (min, max)	0.05000 (0.0500, 2.5800)	-4.19520 (-16.1500, -1.4900)		0.05000 (0.0500, 2.5800)	-4.10760 (-16.1500, -1.4900)	
Hodges-Lehmann estimator	0.05575	-4.49215		0.05575	-4.43500	
95% CI	(0.06310, 0.15087)	(-5.52297, -4.45964)		(0.06327, 0.15455)	(-5.43558, -4.37886)	
Day 336 (V23/EOS)						
n	131	131	<0.001	122	122	<0.001
mean (SD)	0.10650 (0.256015)	-4.82984 (2.840387)		0.08545 (0.186483)	-4.88201 (2.896456)	
median (min, max)	0.05000 (0.0500, 2.0000)	-4.17000 (-16.1500, -0.4600)		0.05000 (0.0500, 2.0000)	-4.13000 (-16.1500, -1.2130)	
Hodges-Lehmann estimator	0.05000	-4.42000		0.05000	-4.43800	
95% CI	(0.06224, 0.15075)	(-5.32081, -4.33887)		(0.05203, 0.11888)	(-5.40116, -4.36285)	

The LH was analyzed as unit IU/L.
*Paired T test or Wilcoxon signed rank test would be used to test the change from baseline for continuous variables.

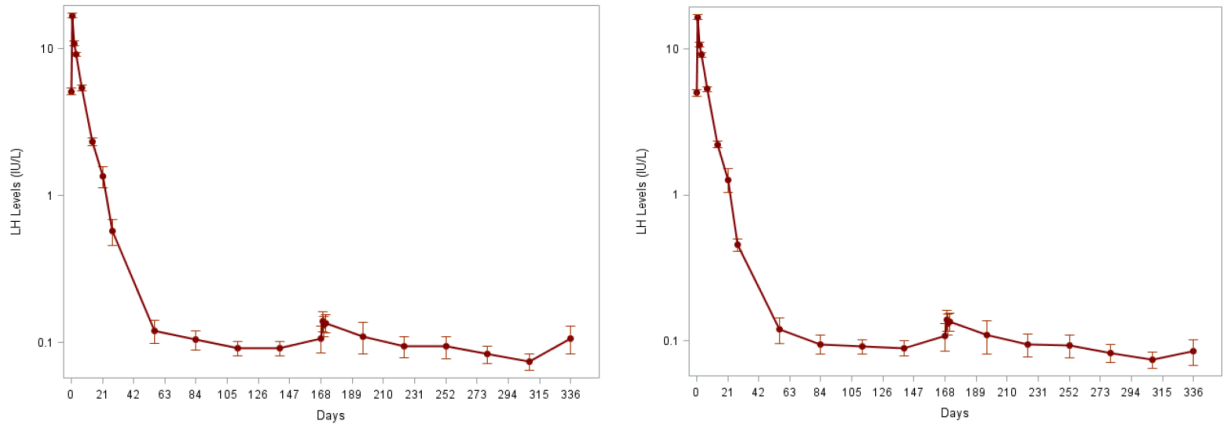
Table 15. Summary of LH levels and change from baseline by PRL lab (ITT and PP populations, Study FP01C-13-001)

	ITT Population (N=137)			PP Population (N=124)		
Variable / Status	Summary	Change	P-value*	Summary	Change	P-value*
Day 0 (V2) - Prior Dosing						
n	137			124		
mean (SD)	9.091 (7.4416)			8.969 (7.2478)		
median (min, max)	6.810 (2.20, 48.61)			6.800 (2.20, 48.61)		
Hodges-Lehmann estimator	7.730			7.670		
95% CI	(7.834, 10.348)			(7.681, 10.258)		
Day 28 (V9)						
n	137	137	<0.001	124	124	<0.001
mean (SD)	0.689 (0.4930)	-8.402 (7.1321)		0.648 (0.3946)	-8.322 (6.9392)	
median (min, max)	0.580 (0.08, 3.90)	-6.300 (-46.87, -1.92)		0.545 (0.08, 2.20)	-6.195 (-46.87, -1.92)	
Hodges-Lehmann estimator	0.600	-7.135		0.590	-7.103	
95% CI	(0.606, 0.772)	(-9.607, -7.197)		(0.578, 0.718)	(-9.555, -7.088)	
Day 168 (V14)						
n	128	128	<0.001	123	123	<0.001
mean (SD)	0.124 (0.1321)	-8.987 (7.5757)		0.124 (0.1343)	-8.753 (7.2096)	
median (min, max)	0.100 (0.07, 1.00)	-6.700 (-48.54, -2.00)		0.100 (0.07, 1.00)	-6.700 (-48.54, -2.00)	
Hodges-Lehmann estimator	0.085	-7.583		0.085	-7.473	
95% CI	(0.101, 0.147)	(-10.312, -7.662)		(0.100, 0.148)	(-10.040, -7.466)	
Day 336 (V23/EOS)						
n	130	130	<0.001	122	122	<0.001
mean (SD)	0.114 (0.1252)	-8.712 (7.0349)		0.108 (0.1007)	-8.790 (7.2187)	
median (min, max)	0.090 (0.07, 1.00)	-6.720 (-48.54, -2.00)		0.080 (0.07, 1.00)	-6.700 (-48.54, -2.00)	
Hodges-Lehmann estimator	0.085	-7.500		0.085	-7.525	
95% CI	(0.092, 0.135)	(-9.933, -7.491)		(0.090, 0.126)	(-10.084, -7.496)	

The LH was analyzed as unit IU/L.
*Paired T test or Wilcoxon signed rank test would be used to test the change from baseline for continuous variables.

Figure 12. Serum LH levels over time from BA lab (Study FP01C-13-001)

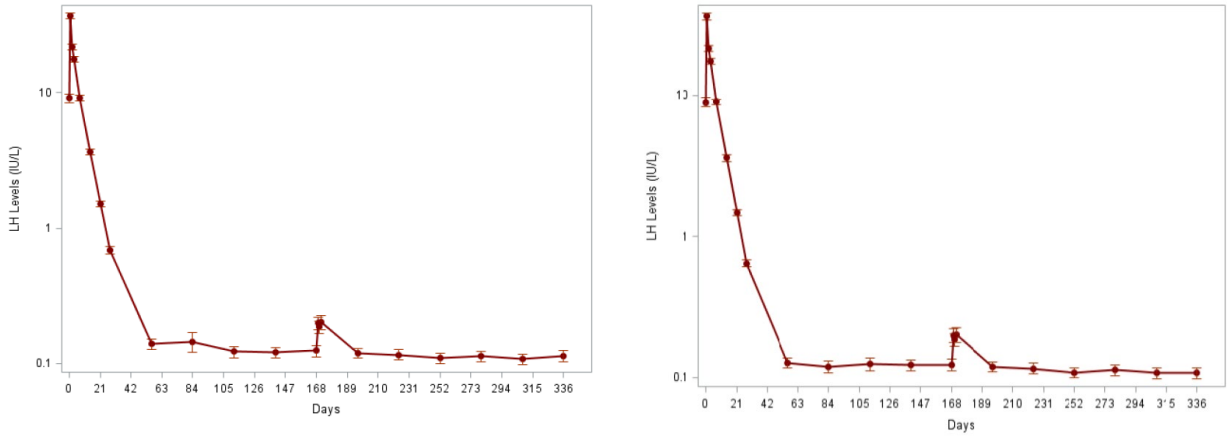
ITT **PP**



ITT = intent-to-treat; PP = per protocol, Source: Study FP01C-13-001

Figure 13. Serum LH levels over time from PRL lab (Study FP01C-13-001)

ITT **PP**



ITT = intent-to-treat; LH = luteinising hormone; PP = per protocol, Source: Study FP01C-13-001

Of 131 PC patients with LH measurements available at End of Study (EOS), 19 patients had increasing LH levels by EOS, when compared to the previous visit. Three patients withdrew from the study and did not receive the second dose of Camcevi, of which two did not achieve either of the efficacy endpoints (serum testosterone levels < 50 ng/dL or PSA < 4 ng/mL on Day 336). The other 17 PC patients with increased LH levels toward the end of study or early termination all achieved the castrated serum testosterone levels below 20 ng/dL and with PSA levels < 4 ng/mL. The mild LH elevation toward the EOS or ET in this subset of subjects did not cause testosterone or PSA increase. No apparent trend with regard to cancer staging, age or body weight was observed between the increasing LH levels by EOS.

Ancillary analyses

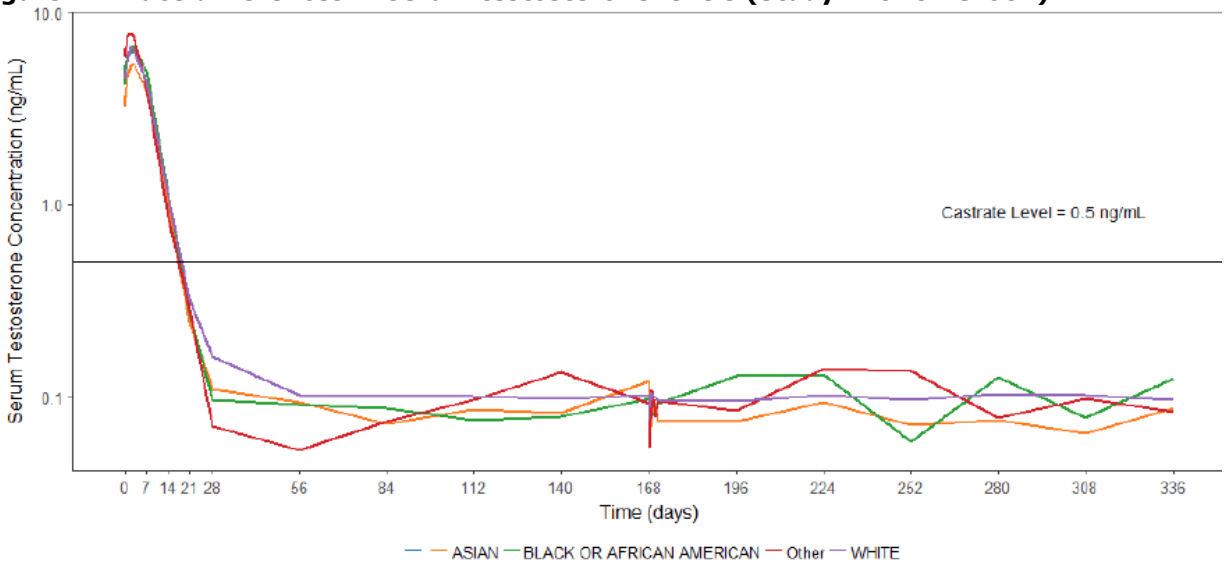
Subgroup analyses:

Subgroup analyses were conducted for the 131 patients in the PK population (refer to Section 3.3.3 of this OV). Analyses included race, Asian vs Non-Asian patients, age, and body weight.

Ethnicity

Median serum testosterone concentration vs. time profiles after subcutaneous administration of LMIS 50 mg on Day 0 and Day 168 by race are presented in Figure 14. These profiles were similar among races with Day 28 levels < 0.5 ng/mL.

Figure 14. Race differences in serum testosterone levels (Study FP01C-13-001)

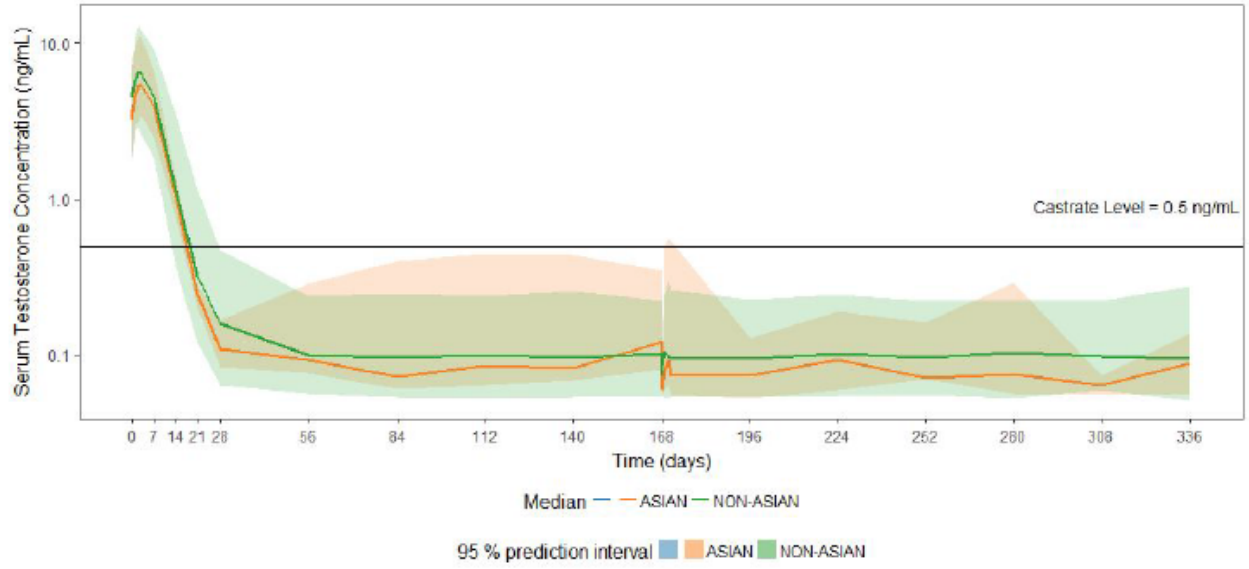


Median serum testosterone concentration vs time after a single subcutaneous dose of LMIS 50 mg (Day 0) or multiple doses (Day 168) by race (semi log scale)

Serum testosterone levels were compared among Asian and non-Asian subjects (

Figure 15). Median serum testosterone concentration time profiles were lower in Asian subjects compared to non Asian subjects. Both groups' median profiles reached the 0.5 ng/mL target levels of testosterone (castrate level) by Day 28, and the level of testosterone remained low until the end of the study (Day 336).

Figure 15. Asian vs. non-Asian serum testosterone levels (Study FP01C-13-001)



Median (95% prediction interval) serum testosterone concentration vs time after a single subcutaneous dose of LMIS 50 mg (Day 0) or multiple doses in Asian and non-Asian (semi-log scale)

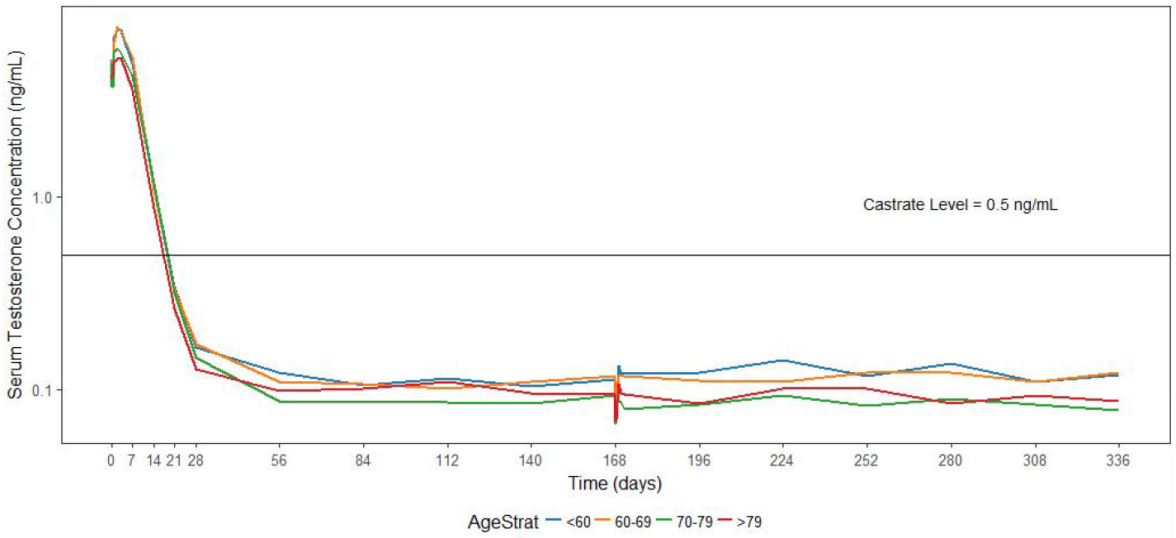
Median serum testosterone concentration-time profiles were lower in Asian patients compared to non-Asian patients at baseline, at D28 and at D336 (EOS), likely attributable to a very limited sample size of Asian subjects (5 patients).

Age

Comparison of testosterone levels by age categories (<60, 60–69, 70–79, or >79 years old) are presented in

Figure 16. Median concentration time profiles for testosterone were comparable among age categories. A similar relationship was observed between serum testosterone concentration levels and age as was seen for serum leuprorelin concentrations.

Figure 16. Age differences in serum testosterone levels (Study FP01C-13-001)



Median serum testosterone concentration vs time after a single subcutaneous dose of LMIS 50 mg (Day 0) or multiple doses (Day 168) by subjects' age categories (semi-log scale).

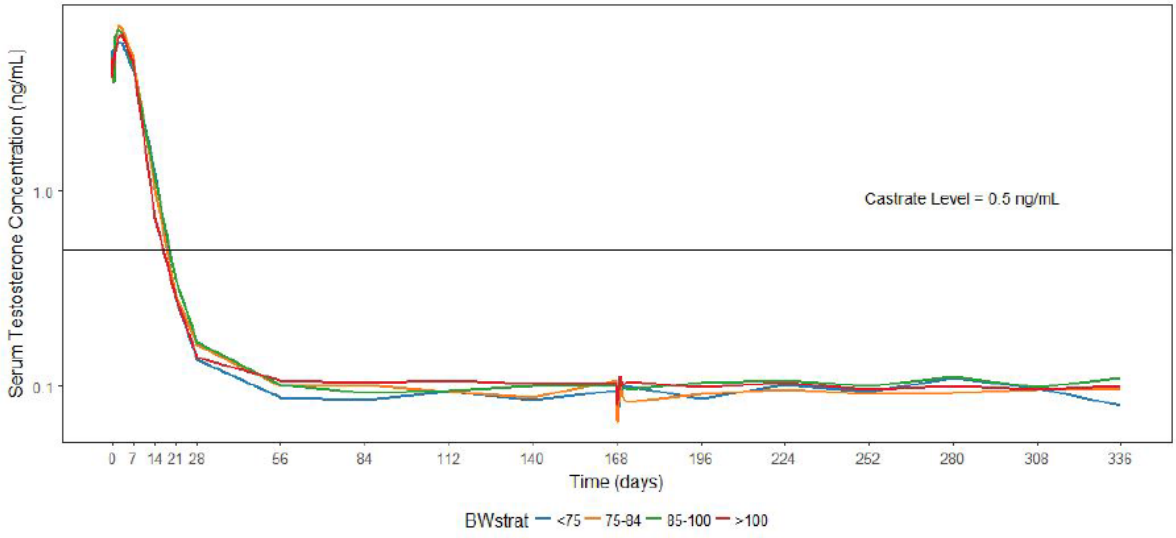
Concerning efficacy, the level of serum testosterone and PSA suppression was not related to age, and not impaired by renal impairment/failure in those 5 PC patients with renal impairment/failure.

Body weight

Comparison of median serum testosterone levels by body weight categories (<75, 75–84, 85–100, or >100 kg) are provided in

Figure **17**. Concentration time profiles were comparable among body weight categories.

Figure 17. Body weight differences in serum testosterone levels (Study FP01C-13-001)



Median serum testosterone concentration vs time after a single subcutaneous dose of LMIS 50 (Day 0) or multiple dose (Day 168) by body weight categories (kg) [semi-log scale].

Detailed analysis by body weight was requested and the results showed that leuprorelin concentrations were within the therapeutic dose range and testosterone levels were below the castrate level in all weight groups, pointing towards that efficacy is achieved also in patients >100 kg with LMIS 50 mg dose.

Summary of main efficacy results

Table 16 summarises the efficacy results from the main studies supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 16. Summary of efficacy for trial FP01C-13-001

Title An open-label, single-arm study of the safety, efficacy, and pharmacokinetic behaviour of leuprorelin mesilate injectable suspension (LMIS 50 mg) in patients with advanced prostate carcinoma			
Study identifier	FP01C-13-001		
Design	Multicentre, open-label, single-arm; 2 parts: Part I for establishing safety prior to enrolment of remainder patients in Part II		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		48 weeks 28 days screening period Not applicable.
Hypothesis	Similarity / therapeutic equivalence to leuprorelin acetate 45 mg (Eligard) – Historical control		
Treatment groups	Male adult patients with histologically confirmed prostate carcinoma, baseline morning serum testosterone level > 150 ng/dL, ECOG performance ≤ 2, within acceptable range of lab chemistry results for lipid profile, serum glucose, HgbA1c, clinical chemistries (K, Na, Mg, Ca, and P), and urinalysis range according to investigator's opinion at screening visit		Treatment: leuprorelin mesilate injectable suspension (LMIS) 50 mg Duration of treatment: every 24-week for total 2 doses Number of patients: 137 patients enrolled (including 33 patients in Part I plus 104 patients in Part II)
Endpoints and definitions	Primary endpoint	%patients TES ≤ 50 ng/dL(D28)	To determine the efficacy of LMIS 50 mg by: percentage of patients with a serum testosterone

		%patients TES ≤ 50 ng/dL(D336)	concentration suppressed to castrate levels (≤ 50 ng/dL) by Day 28 ± 1 (day) following the first LMIS 50 mg injection, and the percentage of patients with serum testosterone suppression (≤ 50 ng/dL) from Day 28 through Day 336 (remaining study duration).
	Secondary endpoint	%patients TES > 50 ng/dL	1. Proportion of patients exhibiting post-suppression excursions of serum testosterone to > 50 ng/dL
	Secondary endpoint	PSA level	2. Effect of LMIS 50 mg on serum PSA levels
	Secondary endpoint	LH level	3. Effect of LMIS 50 mg on serum LH levels
Database lock	05-Jan-2017		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT): Any patient who received at least one dose of LMIS 50 mg. Per protocol (PP): Patients who received 2 doses of LMIS 50 mg and followed the inclusion- / exclusion requirements of protocol without major protocol deviations		
Descriptive statistics and estimate variability	Treatment group	ITT	PP
	Number of patient	137	124
	%patients TES ≤ 50 ng/dL(D28) (%; patient num. without event) 95% confidence interval	98.5% (135 of 137 patients) 94.8-99.8	99.2% (123 of 124 patients) 95.6-100.0
	%patients TES ≤ 50 ng/dL(D336) (%, patient number without event 95% confidence interval)	97.0% (133 of 137 patients) 92.2-98.9	97.6% (121 of 124 patients) 92.7-99.2
Notes	Event was defined as (1) Patients who had testosterone to >50 ng/dL on Day 28 Or, (2) Patients had testosterone to >50 ng/dL from Day 28 through Day 336 Statistical methods: %patients TES ≤ 50 ng/dL (D28) was analysed using standard large sample approximation to a binomial distribution. %patients TES ≤ 50 ng/dL (D336) was analysed using a Kaplan-Meier approach. The duration of time to an event was summarised by Kaplan-Meier plot, and presented as event number, percentage, 95% CI for percentage, mean, median and 95% CI for median. %patients TES > 50 ng/dL were presented as a count, percentage and 95% CI. PSA and LH levels were summarised by descriptive statistics, and the change from baseline was summarised descriptively and a paired t-test or Wilcoxon signed-rank test was used with significance level of 0.05.		
Notes **Analysis description**	**Secondary analysis** The definition of population is the same as in primary analysis. **1. %patients TES > 50 ng/dL**: Though 2 patients exhibited the post-suppression excursion of serum testosterone to > 50 ng/dL after achieving castration level on Day 28, which were due to acute-on-chronic surge following second LMIS 50 mg administration, the % of patients exhibiting post-suppression excursion of serum testosterone to > 50 ng/dL was 0% in both ITT and PP populations at the end of study (Day 336/V23). **2. Effect of LMIS 50 mg on serum PSA levels** Mean baseline of PSA levels in ITT were 84.747±382.4744 ng/mL on Day 0 (V2), and it decreased to 21.709±80.9601 ng/mL on Day 28 (V9), 5.017±18.4060 ng/mL on Day 84 (V11). It appeared to approach the normal level on Day 168 (V14) with mean PSA level of 2.577±7.5404 ng/mL. A slight increase of mean PSA levels was observed on Day 252 (V20) with a mean PSA level of 3.545±13.0604 ng/mL and this increase was also observed at the end of study on Day 336 (V23/EOS) with a mean PSA level of 12.837±65.5957 ng/mL. A similar effect of LMIS 50 mg on serum PSA levels was observed in PP. Administration of LMIS 50 mg significantly reduced the serum PSA levels from Day 28 until the end of study. Although a mild rebound in PSA levels was observed from Day 252 to Day 336 (V23/EOS), the mean serum PSA levels remained low and significantly lower than the baseline value. **3. LH levels**: In ITT, mean LH level at baseline was 5.125±3.0421 IU/L and as expected an		

acute increase of mean serum LH level to 16.813±8.0169 IU/L on Day 1 (V3) was observed after the first administration of LMIS 50 mg. A rapid decrease of serum LH levels was observed on Day 2 (V4) with a mean level of 10.8721±4.39251. The serum LH levels continued to decrease from Day 3 (V5) with mean LH level of 9.170±3.7546 until it approached a plateau on Day 140 (V13) with mean LH level of 0.09146±0.116426. On Day 168 (V14), the mean serum LH level was 0.10699±0.251897 IU/L and a slight increase of serum LH level to 0.14016±0.252015 IU/L was observed again on Day 169 (V15) after the second administration of LMIS 50 mg. Continuous decrease of mean serum LH level was observed subsequently from Day 170 (V16, 0.13081±0.232549 IU/L) until Day 308 (V22, 0.07420±0.103575 IU/L). A slight increase in mean LH level was observed at the end of study on Day 336 (V23/EOS, 0.10650±0.256015 IU/L).
Similar results of serum LH level were observed in PP.
Administration of LMIS 50 mg significantly reduced the serum LH levels after its first injection and this effect remained until the end of study.

Treatment group	**ITT**	**PP**
Number of patients	**137**	**124**
%patients TES > 50 ng/dL (Day 336) (%, event number) 95% confidence interval)	0% (0 of 129 patients) 0.0-2.8	0% (0 of 121 patients) 0.0-3.0
PSA levels	See "Notes"	See "Notes"
LH	See "Notes"	See "Notes"

Clinical studies in special populations

Elderly population

The pivotal study protocol enrolled male patients who were over ≥ 18 years old.

	Age 65-74 (Older patients number /total number)	**Age 75-84 (Older patients number /total number)**	**Age 85+ (Older patients number /total number)**
Non Controlled trials	51/137	45/137	6/137

Children and adolescents

Patients <18 years were not included in the study.

Renal and hepatic impairment

Patients with renal and hepatic impairment were included in the study as follows:

- 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.

2.6.5.3. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.6.5.4. Supportive study(ies)

Efficacy results from the published literature:

Five studies from the published literature were identified in support of 6-month leuprorelin depot forms in the treatment of prostate cancer, including the main study supporting efficacy and safety of Eligard 45 mg (Crawford et al., 20068). The published clinical studies on leuprorelin 6-month were selected as being relevant for the applicant's clinical Study FP01C-13-001, corresponding in design and methodology with the comparable studies retrieved. These published efficacy and safety studies of leuprorelin 6-month depot in prostate cancer were conducted with either Atrigel or Eligard.

All studies evaluated the pharmacodynamic efficacy of 2 doses of 45 mg leuprorelin acetate depot for 12 months (48 weeks). A suppression in testosterone to below castrate levels (≤ 50 ng/dL) was reported in all studies in at least 93% of patients (Crawford et al., 2006; Spitz et al., 20129; Mostafa et al., 201410; Shore *et al*., 2017[11]). The highest percentage reported was 99%, where 102 of 103 patients were below castrate levels (Crawford *et al*., 2006). For studies that used a more rigorous threshold of ≤ 20 ng/dL, 86.0% to 94.1% of patients were suppressed to below these levels through the end of the 1-year study (Crawford *et al*., 2006; Spitz *et al*., 2012; Shore et al., 2017). The percentage of patients with suppression of testosterone below castrate levels in the published literature is similar to the results obtained in the Sponsor-conducted Study FP01C-13-001. Refer to Table 17

[8] Crawford ED, Sartor O, Chu F, Perez R, Karlin G, Garrett JS. A 12-month clinical study of LA-2585 (45.0 mg): a new 6-month subcutaneous delivery system for leuprolide acetate for the treatment of prostate cancer. J Urol 2006;175: 533-536.

[9] Spitz, A., Young, J.M., Larsen, L., Mattia-Goldberg, C., Donnelly, J., and Chwalisz, K. (2012). Efficacy and safety of leuprolide acetate 6-month depot for suppression of testosterone in patients with prostate cancer. Prostate Cancer Prostatic. Dis. *15*, 93-99.

[10] Mostafa NM, Chwalisz K, Larsen L, Mattia-Goldberg C, Spitz A, Pradhan RS. Evaluation of the pharmacokinetics and pharmacodynamics of two leuprolide acetate 45 mg 6-month depot formulations in patients with prostate cancer. Clin Pharmacol Drug Dev. 2014;3: 270-275.

[11] Shore, N.D., Chu, F., Moul, J., Saltzstein, D., Concepcion, R., McLane, J.A., Atkinson, S., Yang, A., and Crawford, E.D. (2017). Polymer-delivered subcutaneous leuprolide acetate formulations achieve and maintain castrate concentrations of testosterone in four open-label studies in patients with advanced prostate cancer. BJU Int. *119*, 239-244.

Table 17. Efficacy data for prostate carcinoma patients treated with leuprorelin acetate 45 mg, 6-month depot formulations from published literature studies

Reference	Treated Population	Dose	Treatment Duration	Efficacy Findings
(Tunn, 2011; Ohlmann and Gross-Langenhoff, 2018)	n = 1273 mean age 75 years (range 50–97)	Eligard® 45 mg, SC injection, once every 6 months	12 months	• Median PSA values decreased by 94% from 11.6 to 0.7 ng/mL in the first 6 months. PSA decreased even further to 0.5 ng/mL at the end of the study (a 96% decrease). • Testosterone measurements were available for 350 patients. Median concentrations decreased from 89 to 10 ng/dL during the first 6 months, decreased even further to 9 ng/dL at the end of the study (a 90% decrease).
(Shore et al., 2017)	n = 111 mean age 73.2 years (range 53–84)	Eligard® 45 mg SC injection, once every 6 months	48 weeks	• Mean testosterone concentrations were decreased from 367.7±13.0 ng/dL at baseline to 16.7±3.4 at 1 month, 10.4±0.5 at 3 months, 10.4±0.5 at 6 months, and 12.6±2.1 at the end of the study. Four patients (3.6%) were above the castrate threshold at the end of the study. • LH concentrations were consistently below 1 IU/L by day 7 through the remainder of the study. • PSA baseline values were reduced by 97% at the end of the study.
(Spitz et al., 2012; Spitz et al., 2016)[a]	n = 148 mean age 74.9 years (range 48–84)	Leuprorelin acetate 45 mg, intramuscular injection, once every 24 weeks	48 weeks	• Of the original 151 patients, 148 were included for the efficacy analysis. • Serum testosterone was suppressed to below castrate levels (50 ng/dL) from week 4 through week 48 in 93.4% of subjects. At 48 weeks, 94.1% were suppressed ≤ 20 ng/dL. Levels remained ≤ 11 ng/dL at the end of each treatment cycle. Of the 8 testosterone escapes, 4 occurred in patients who were African American and none were associated with increases in PSA. • Subjects with more advanced prostate cancer (stage IV) had a significantly higher rate of response to treatment (100% vs 91.8%, p = 0.003). • At baseline, 75% of subjects had baseline serum PSA concentrations that were > 4 ng/mL. There was a transient rise in mean serum PSA concentrations after the first injections. Within 14 weeks, 87.4% of these subjects achieved a PSA of ≤ 4 ng/mL. At all subsequent visits, at least 86% of the subjects had a PSA of ≤ 4 ng/mL.

Reference	Treated Population	Dose	Treatment Duration	Efficacy Findings
(Mostafa et al., 2014)[a]	n = 302 mean age 75.8 years (range 56–92)	Leuprorelin acetate 45 mg (2 unspecified formulations, A and B), subcutaneous injection, once every 6 months	48 weeks	• The concentration-time profile for testosterone and LH for both formulations showed an initial increase after the first injection. • Testosterone and LH concentrations decreased continuously to reach a low plateau by week 4, which was maintained through the end of the study. There were no changes in concentrations with the second leuprolide acetate injections. The mean percentage of subjects that showed suppression of serum testosterone ≤ 50 ng/dL from week 4 through 48 was 93.4% (90% confidence interval 89.9–96.9) for formulation A. • A larger number of subjects receiving formulation B escaped from testosterone suppression and that arm of the study was prematurely terminated.
(Crawford et al., 2006)	n = 111 mean age 73.2 years (range 50–86)	Eligard® 45 mg, subcutaneous injection, once every 6 months	12 months	• Of the original 111 patients, 103 completed the 12-month study. • Mean time to castrate suppression was 21.2 days (median 21). At study completion, 102/103 patients (99%) were below medical castrate testosterone levels, with 91/103 (88%) less than 20 ng/dL. • Mean LH decreased from 6.98 ± 0.48 mIU/mL at baseline to below baseline by day 7. Mean LH then decreased consistently throughout the first 19 weeks to 0.1 ± 0.01 mIU/mL at day 133. LH levels at month 12 were 0.23 ± 0.14 mIU/mL. • Mean PSA decreased 97% from 39.8 ± 21.5 ng/mL at baseline to 1.2 ± 0.3 ng/mL at 12 months.

AE = adverse event; FSH = follicle-stimulating hormone; LH = luteinising hormone; PSA = prostate specific antigen; SAE = serious adverse event; SC = subcutaneous; SD = standard deviation

Usability of Pre Filled Syringe (PFS) :

The applicant submitted usability data including use-related risk analysis (URRA), Threshold analysis and a review of Phase III study data during the MAA evaluation procedure. The provided data supported safe and effective use of Camcevi PFS device in the intended use environment. Due to fewer preparatory steps (lack of reconstitution/mixing steps) before injection, it can be presumed that handling errors will occur less likely with Camcevi PFScompared to Eligard.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal efficacy study (FP01C-13-001) conducted with LMIS 50 mg, was a single clinical Phase 3, uncontrolled, multicentre, open-label, single-arm, 12-month, two-part PK, safety and PD/efficacy study performed in 137 male patients with prostate carcinoma in need for androgen deprivation therapy (male adult patients with histologically confirmed prostate carcinoma, baseline morning serum testosterone level > 150 ng/dL, ECOG performance ≤ 2). Patients were scheduled to receive two doses of LMIS 50 mg, 6 months apart. The study was conducted in USA, Europe, and Taiwan. The study was conducted in 2 parts. Part I included the first 30 subjects, who had more frequent monitoring for safety. Once ≥90% of the 30 subjects achieved suppression of serum testosterone concentrations to castration levels (≤50 ng/dL) within 28 days of the initial dose, with acceptable safety and tolerability, Part II was opened, and the rest of the subjects were enrolled.

In terms of clinical pharmacology, efficacy and safety, the applicant relies on data of the reference product Eligard 45 mg, which was approved in EU in Germany first in 2006. The MAA for LMIS 50 mg (Camcevi 42 mg) was submitted under Article 10(3) of Directive 2001/83/EC. For the marketing authorisation approval of this hybrid application, the bridging between LMIS 50 mg and the EU-sourced reference product Eligard 45 mg is needed. As the same clinical study (Study AGL-0205) was the pivotal registration study for Eligard 45 mg to support both the New Drug Application (NDA) in the US and MAA in Europe through a mutual recognition procedure, and Germany (BfArM) serving as RMS in the original submission of Eligard 45mg. it is agreed that a bridging of LMIS 50 mg data to Eligard 45mg data can be made based on pharmacodynamic response, i.e., suppression of testosterone levels. The bridging can also be supported by non-clinical findings and clinical pharmacokinetic findings. In addition, the *in vitro* release data can only be considered as supportive for the bridge due to the complex formulation of the products.

A review of published literature for the efficacy and safety of 6-month leuprorelin depot forms in palliative treatment of prostate cancer was included. Five non-comparative, open-label studies were identified, all of which evaluated at least PD on serum testosterone levels over 12 months as per effects of two injections of 45-mg leuprorelin acetate depot forms.

The primary efficacy endpoint was the suppression of serum testosterone levels below castrate levels (≤ 50 ng/dL) by Day 28 ± 1(day) following the first injection of LMIS 50 mg and the percentage of patients with serum testosterone suppression (≤ 50 ng/dL) from Day 28 through Day 336 (remaining duration of the study).

The secondary efficacy endpoints included post-suppression elevation of serum testosterone (> 50 ng/dL), serum PSA levels, and serum LH levels. PSA and LH are considered additional assessments of efficacy, as PSA is a marker for prostate cancer and LH production is upstream of testosterone.

Clinical study design and endpoints are acceptable for documenting the biological activity and safety of the proposed formulation of leuprorelin. For demonstration of a bridge between LMIS 50mg and EU-Eligard 50mg, the performance of a single arm study is acceptable, provided that the bridge to the reference product data is shown.

On the clinical efficacy side, the main purpose of the trial was to demonstrate the biologic activity and safety of LMAS 50mg. Baseline clinical characteristic and detailed staging information of patients in the LMIS main study compared with those of the studies of the comparator Eligard, mainly the pivotal Eligard 45 mg study (Crawford et al., 2006) to justify the bridging of the LMIS 50 mg clinical data to

Eligard 45 mg clinical data were presented. The data provided for the purpose of demonstration of a bridge between LMIS 50mg and EU-Eligard 45 mg is considered acceptable.

Based on data provided, it can be concluded that the inclusion and exclusion criteria in LMIS 50mg and Eligard 45 mg studies are relatively similar. With very broad inclusion criteria, and also taking into consideration the prostate cancer treatment developments over time, it is well understood that patient characteristics included in these two studies may vary, which can be seen while comparing the baseline characteristics of the patients in these two studies. The baseline classification of the patients in the LMIS 50 mg study is hampered by the lack of Gleason score, which was not collected in the study, and by missing staging information in a substantial number of patients. Even though the multiple issues concerning the comparability of the patient populations in these two studies could not be fully clarified, they were not pursued further as they do not impact the validity of the results.

The study was conducted in two parts as described above. Continuous variables were described using descriptive statistics. For missing data, no method of imputation was applied. The paired T test or Wilcoxon signed rank test was used to test the change from baseline. No adjustments for covariates were performed in this study. No multiple comparisons were performed.

A sample size of 120 patients was estimated to achieve the 85% power to detect a difference of 0.0700 using a one-sided binomial test. A pre-specified interim analysis of efficacy was performed after 100 patients had completed the Day 28 assessment and a sample size reassessment was carried out to determine whether additional patients needed to be enrolled. The estimated conditional power was 99.07%. Thus, the trial continued as planned with the current sample size. A total of 137 patients were enrolled in the study at the end.

Three populations were analysed: ITT, PP, and safety populations.

The definitions of analysis populations follow the conventions in clinical trials, and as such are considered acceptable. For missing data related to a safety or efficacy endpoint, no method of imputation was applied. For the primary efficacy endpoint, the drop-out and missing values were handled by specific censoring rules. Sensitivity analyses were performed for serum testosterone levels ≤50 ng/dL and post hoc analysis was performed in the patients with elevated PSA at baseline.

Of the 137 patients enrolled in the study, 122 completed the study treatment. In total, 15 patients discontinued study, the most common reasons being an AE (n=5), withdrawal of the consent (n=3) or use of prohibited medication (n=4). One patient discontinued due to lack of efficacy, one due to disease progression (PSA increase) and one patient was lost to follow-up. In general, the numbers or discontinued patients were considered to be acceptable, and the reasons for discontinuations typical for the study population. The discontinuations are not expected to influence efficacy conclusions as efficacy analyses were performed both with ITT and PP population.

The study protocol was amended four times. The original Protocol was dated 24-Mar-2014 and the latest version 1.4 was dated 14-Oct-2015. The applicant submitted the protocol versions and descriptions of the protocol amendments. The amendments concerned various sections including efficacy, safety, pharmacokinetics and statistical analyses. The applicant states, that no changes were made in the conduct of the study or planned analyses and the study was performed in accordance of the study protocol FP01C-13-001 version 1.4, dated October 14, 2015, which can be accepted.

All together 452 protocol deviations were reported, of which 14 incidences in eleven patients were reported as major deviations. As the efficacy analyses were performed both with ITT and PP populations, the major deviations did not affect the efficacy results. The deviations were mainly considered procedural deviations and related to Good Clinical Practice compliance, or related to the use of prohibited medicines. As such these major deviations are not considered to affect the efficacy or safety assessment of LMIS 50 mg.

The minor deviations comprised missing information in reporting of, *e.g.*, VAS scale, incorrect sampling time, incorrect measuring of, *e.g.*, ECG and temperature, and unperformed biochemistry sampling. Also, some of the PK, testosterone and LH samples were frozen or defrosted before analysis or study visits were conducted on incorrect days.

Five interim safety reviews and one interim analysis of efficacy were conducted during this study, which were overseen by an independent data monitoring committee (IDMC) and an independent statistical centre (ISC). The interim analysis was not intended for use in a decision to stopping the trial and claiming that statistical significance has been achieved, but rather to guarantee that study's statistical power would be achieved.

Efficacy data and additional analyses

The Part I and Part II populations were comparable and the differences observed were not clinically relevant.

Baseline characteristics

Despite uncertainties as to the actual numbers of patients with different disease extent classification of the included population, it is assumed that these uncertainties, do not present significant bias on the primary endpoint estimates.

There were 83.2% (114/137) patients with Grade 0, 16.1% (22/137) patients with Grade 1, and 0.7% (1/137) patient with Grade 2 ECOG performance status. Thus, the majority of the patients were in good fit with relatively little symptoms. The population included represented a subset of patients for whom leuprorelin was indicated as a therapeutic approach.

Therapies that were allowed during the study were acceptable as part of good care and they are not considered to affect the efficacy results. The majority of the patients had some current medical condition, which covered common cardiovascular diseases and other conditions reflecting the population seen in clinical practice.

The presented tumours histories covered common localised tumours in men. The most common previous treatments included radical prostatectomy and radiotherapy and antiandrogen therapy, as expected. Also, treatment of previous cancer other than prostate cancer were reported. About 55% of subjects in the study had received prior treatment with different therapies and combination of therapies, whereas about 45% had not received any treatment for their PC. Thus, the majority of the patients had received previous treatment for their prostate cancer with curative intent, which has affected the course of the prostate cancer and possibly the response to the antiandrogen therapy with LMIS 50 mg.

Radiotherapy to the prostate as part of a multimodality assessment was not explored even though as a bridge is requested for this indication. On the same lines, "*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"* was not allowed according to exclusion criteria, which raised concerns about potential under-treatment of patients. Exclusion of these treatments was considered by the applicant as pertinent to prevent potential bias in the efficacy assessment for LMIS 50 mg alone in reducing testosterone and PSA levels in PC patients who are received other therapies This rationale can be followed and the explanations are considered acceptable.

Primary endpoint of testosterone levels

The primary efficacy endpoint was to determine the percentage of patients with a serum testosterone concentration suppressed to castrate levels (≤ 50 ng/dL) by Day 28 ± 1 (day) following the first

injection of LMIS 50 mg and the percentage of patients with serum testosterone suppression (≤ 50 ng/dL) from Day 28 through Day 336 (remaining duration of the study).

The efficacy endpoints were designed to be in line with the reference product Eligard 45 mg. The analysis of the primary efficacy endpoint revealed that the percentage of patients with a serum testosterone of ≤ 50 ng/dL (castrate level) by Day 28 was 98.5% in the ITT population and 99.2% in the PP population with LMIS 50 mg. The percentage of patients with testosterone suppression from Day 28 through Day 336 was 97.0% in the ITT population and 97.6% in the PP population. These results, as well as those based on evaluation of secondary endpoints, can be considered to be similar to those obtained with Eligard 45 mg, even though the evaluation is hampered by the lack of comparative data. However, based on the totality of evidence, the selected bridging approach of LMIS 50 mg to Eligard 45 mg without comparative data can be considered acceptable.

There were two patients who did not reach the castrate levels on Day 28 of which one due to lack of efficacy (did not receive the second dose) and the other one completed the study achieving castrate levels at later time point Day 56 (received the second dose). Other two patients, , experienced post-suppression excursions of testosterone to >50 ng/dL, following the second dose of LMIS 50 mg, which were concluded to be related to the acute-on-chronic excursion of LH. In addition to these episodes, no other elevations were reported. The testosterone surge (flare) did not appear to be associated with significantly increased PSA, disease progression, or adverse events. Based on the narratives of these cases No unexpected findings were found.

Subgroup analyses on the effect of cancer stage, time from diagnosis to date of informed consent, body weight and age to the serum testosterone levels and the suppression rate were performed. However, as there were only a limited number of patients, who did not reach the castrate levels, no conclusions based on these subgroup analyses could be made.

Secondary endpoints

The secondary endpoints included the proportion of patients 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" phenomenon (*i.e.*, related to the second dose of LMIS 50 mg). No "breakthrough" episodes were reported. Two patients exhibited post-suppression elevated castrate levels of testosterone (> 50 ng/dL) during the study. As for the primary endpoint results, also the secondary endpoint results were comparable with the reference product.

Regarding the more stringent suppression level of testosterone, LMIS 50 mg and Eligard 45 mg were comparable towards the EOS.

PSA levels

The administration of LMIS 50 mg reduced the serum PSA levels after the first injection compared to the baseline level until the end of the study in ITT and PP populations. In the ITT population, mean baseline of PSA levels were 84.747±382.4744 ng/mL on Day 0, and level decreased to 2.577±7.5404 ng/mL by Day 168 after the first dose. The range of PSA was considerably wide from baseline (0.06-2748.44), to Day 28 (0.06-525.91), to Day 168 (0.06-56.56), and to EOS Day 226 (0.06-318.05).

A similar effect of LMIS 50 mg on serum PSA levels was observed in the PP population. The mean baseline PSA levels were 70.240±333.4071 ng/mL on Day 0 and 2.641±7.6833 ng/mL at Day 168 after the first dose. The range of PSA was similarly wide from baseline (0.06-2748.44), to Day 28 (0.06-635.79),), to Day 168 (0.06-56.56), and to EOS Day 226 (0.06-644.57).

Overall, the discrepancy between the mean and median levels underline the wide range of PSA levels, which in turn reflect the heterogeneity in the tumour biology and the prostate cancer trajectory of the study population.

However, an increase of mean PSA levels was observed from Day 252 onwards with a mean PSA level of 3.545±13.0604 ng/mL and with increasing levels towards EOS on Day 336 with a mean PSA level of 12.837±65.5957 ng/mL in ITT population. A similar effect of LMIS 50 mg on serum PSA levels was observed in the PP population. An increase of mean PSA levels was observed on Day 252 with mean PSA level 3.620±13.2136 ng/mL on Day 252 and at EOS on Day 336 with mean PSA level of 7.972±37.1654 ng/mL. This PSA increase ranged from slight (without clinical relevance) to significant increase. For Eligard 45 mg, PSA steadily decreased and by EOS only 4 of 103 (2.9%) patients had elevated PSA level.

The applicant reported this result as a mild rebound in PSA levels from Day 252 to Day 336 (V23/EOS). Transient rise ("bounce") of PSA after prostate surgery and radiotherapy is a common phenomenon and it is not connected to worsening of the prognosis of prostate cancer. Some studies refer that this post-treatment brief rise is connected to improved prognosis. The current understanding is that the brief rise of PSA results from the release of PSA from destroyed cancer cells or from normal prostate tissue exposed to radiotherapy. This brief rise can occur up to 1-3 years after the given radiotherapy, which fits to the mechanism of action of radiotherapy (direct and indirect action of radiation on the DNA molecules). However, this is not the case in the elevations of PSA in the current study.

The rise in PSA levels for the EOS raised concerns about efficacy.

As discussed in detail in the pharmacodynamic section, the rise in the PSA levels towards the end of study may be related to the higher PSA levels at baseline compared to the Eligard and other studies, as well as the slightly different patient populations included in these two studies. However, due to lack of comparative data, no conclusions based on PSA levels can be made. Nevertheless, the results concerning the primary endpoint, i.e., the testosterone suppression, was similar with LMIS and Eligard irrespective of these difference in the PSA values.

LH levels

The administration of LMIS 50 mg with six months dosing interval reduced the serum LH levels below the baseline after the first injection, and this effect remained until the end of the study. However, two types of increase in the LH levels were observed; transient increase following every injection of LMIS 50 mg and slight increase towards the end of the study. The same transient increase in mean LH levels was observed also following Eligard 45 mg. A continuous decrease of mean serum LH level was observed subsequently from Day 170 until Day 308 and the increase occurred thereafter towards the end of study on Day 336 observed both in ITT and PP populations as well as in the BA Lab and PRL Lab. Thus, a slight increase in mean LH level was observed at EOS on Day 336 in 17 patients with available data and in three cases LH level increased > 1.0 IU/L.

The mild LH elevation toward the EOS or ET in this subset of subjects did not cause testosterone or PSA increase. No apparent trend with regard to cancer staging, age or body weight was observed between the increasing LH levels by EOS.

Ancillary analyses and supportive studies

The comparison of serum testosterone levels between different races showed similar PK-profiles. However, median serum testosterone concentration-time profiles were lower in Asian patients compared to non-Asian patients. Both groups' median profiles reached the 0.50 ng/mL target levels of testosterone (castrate level) by Day 28, and the level of testosterone remained low until the end of the study (Day 336). . As there were only five Asian patients, no conclusions based on these low numbers can be made.

Median concentration-time profiles for testosterone were comparable among age categories (< 60, 60-69, 70–79, or > 79 years old). A similar trend as seen with age and leuprorelin concentration was seen for age and testosterone concentration, so that higher age led to higher leuprorelin concentrations and further to lower testosterone concentrations. The mean testosterone concentrations levels were below the castrate level in all patient groups through the study period. The effect of LMIS 50mg to suppress serum testosterone and PSA levels was not related to age. Concentration time profiles for testosterone were comparable among body weight categories (< 75, 75–84, 85–100, or > 100 kg). Yet, a trend is seen, that higher body weight results in higher testosterone levels.

The effects of LMIS 50 mg to suppress serum testosterone and PSA levels were not impaired by the renal impairment/failure in those 5 PC patients with renal impairment/failure. These low numbers of patients with renal impairment do not allow meaningful conclusions.

Five studies from the published literature were identified in support of 6-month leuprorelin depot formulations in the treatment of prostate cancer, including the main study supporting efficacy and safety of Eligard 45 mg. The applicant provided a short summary of conclusions and deemed results of the current pivotal Phase 3 study to be similar to the results found in the published literature which can be agreed. broadly agreed. The selection of the studies is considered acceptable.

LMIS 50 mg is supplied in a sterile, ready-to-use single syringe. The applicant provided data that supported safe and effective use of PFS in the intended use environment.

2.6.7. Conclusions on the clinical efficacy

The applicant has conducted a single clinical Phase 3 trial with LMIS 50 mg, which was an uncontrolled, multicentre, open-label, single-arm, 12-month, two-part PK, safety and PD/efficacy study in 137 males with prostate carcinoma in need for androgen deprivation therapy. In terms of clinical pharmacology, efficacy and safety, the submission relies on data from the reference product Eligard 45 mg, which in EU was first approved in Germany in 2006.

Based on the information that the same clinical study for Eligard 45 mg was used to support the New Drug Application (NDA) in the US, and MAA in Europe through a mutual recognition procedure and Germany serving as Reference Member State it is accepted that a bridging of LMIS 50 mg data to Eligard 45mg data can be made.

The bridging is based on pharmacodynamic responses of testosterone suppression, and comparison of *in vitro* release characteristics of EU-sourced Eligard 45mg and LMIS 50mg; non-clinical findings and clinical pharmacokinetic findings are considered supportive.

The study population appears to be rather heterogeneous with regards to the prostate cancer disease extent and previous anticancer treatments. However, since the study was designed to assess pharmacodynamic endpoints, the inclusion of heterogenous PC patients, in need for LHRH-targeted medications, is acceptable for the purpose of this procedure.

The efficacy endpoints were designed to be in line with the reference product Eligard 45 mg. Overall, the study met the primary and secondary endpoints and the results were comparable with the reference product.

The observed changes in the serum testosterone, LH and PSA levels towards the end of study were relatively infrequent, and based on data presented can be mainly deemed to be related to patient-related reasons and not due to loss of efficacy towards the end of the 6 months dosing interval. The lacking baseline staging information in a large number of patients raises concerns about study conduct,

but is not expected to jeopardize the primary endpoint assessment, i.e., the testosterone suppression levels.

2.6.8. Clinical safety

Safety data for this application come from the pivotal study FP01C-13-001 where safety and tolerability of LMIS 50 mg were listed as primary endpoint. Complementarily, publications from other trials and FDA adverse event reporting system (FAERS) data have been submitted. In addition to data from the FAERS database (which is considered only supportive), the EU data originating from the EudraVigilance were provided (See "Published literature and databases"). The primary outcome measures for the FP01C-13-001-EX were AEs, clinically significant changes in ECGs and laboratory parameters (haematology, biochemistry and urinanalysis).

The formulation of LMIS 50 mg contains N-methylpyrrolidone (NMP) and poly (D,L-lactide) (PLA) as excipients. Both of these are already contained in medicinal products for parenteral use in the EU.

2.6.8.1. Patient exposure

In Study FP01C-13-001, 137 patients were exposed to LMIS 50 mg and 128 patients received 2 doses. Almost 90% of enrolled patients were white.

Two PK studies were performed during the clinical development programme. Study FSEE-CSC-100 included patients from Study FP01C-13-001, and Study FSEE-PMX-FP001-1605 included data from FP01C-13-001 as well as from Eligard 45 mg reports. The safety findings of the PK analyses performed by the applicant are included in FP01C-13-001 safety data.

Overall, 95.6% of patients used concomitant medications (data not shown).

2.6.8.2. Adverse events

Study FP01C-13-001 began with 30 patients undergoing frequent safety monitoring (Part I). In addition, the first 10 patients of this group were under more frequent monitoring for safety endpoints. Eventually, 33 prostate cancer patients were enrolled in Part I. Of them four patients did not complete the study (12%), due to protocol deviation, disease progression, withdrawal of consent due to lack of efficacy or withdrawal of consent. Eventually altogether 137 patients were enrolled, 122 completed the study and 15 withdrew (11%), with the most common reason for withdrawal an AE (5 patients). Other reasons were lack of efficacy (1), lost to follow-up (1), disease progression (1), withdrew consent (3), treated with prohibited medications due to medical need (3) or taking Humalog 18 units TID (1).

Summary of the TEAEs is presented in Table 18

Table 18. Summary of TEAEs and drug related AEs (ADRs) in Study FP01C-13-001

	Part I (N=33)			Part II (N=104)			Total (N=137)		
Variables \ Status	**Event**	**Subject**	**(%)**	**Event**	**Subject**	**(%)**	**Event**	**Subject**	**(%)**
TEAEs									
Total	160	31	(93.9%)	393	83	(79.8%)	553	114	(83.2%)
TEAEs by severity									
Mild	116	29	(87.9%)	279	76	(73.1%)	395	105	(76.6%)
Moderate	36	19	(57.6%)	94	40	(38.5%)	130	59	(43.1%)
Severe	6	5	(15.2%)	18	13	(12.5%)	24	18	(13.1%)
Death	2	1	(3.0%)	2	2	(1.9%)	4	3	(2.2%)
TEAEs by relationship									
Definite	18	13	(39.4%)	38	26	(25.0%)	56	39	(28.5%)
Possible	26	17	(51.5%)	62	46	(44.2%)	88	63	(46.0%)
Unrelated	116	27	(81.8%)	293	68	(65.4%)	409	95	(69.3%)
Drug-related AEs*									
Total	44	21	(63.6%)	100	64	(61.5%)	144	85	(62.0%)
Drug-related AEs* by severity									
Mild	35	19	(57.6%)	81	56	(53.8%)	116	75	(54.7%)
Moderate	7	5	(15.2%)	18	13	(12.5%)	25	18	(13.1%)
Severe	2	2	(6.1%)	1	1	(1.0%)	3	3	(2.2%)
SAEs									
Yes	7	6	(18.2%)	27	14	(13.5%)	34	20	(14.6%)

The AE percentage: 100%*the number of subjects with event (n) / Total number of subjects in Safety Population (N)
For subject with the same AE but multiple different severity/relationship (which resolution date = onset date or resolution date = onset date + 1, except they had different AE No.), the multiple events would be combined as one AE with the maximum severity/relationship category for analysis.
*Causal relationship to study drug: AEs related to study drug include AEs classified as 'Possible', 'Probably', or 'Definite'. AEs not related to study drug include AEs that were 'None' or 'Improbable'.
AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event

In FP01C-13-001, most common TEAEs are presented in Table 19 by PT and with ≥5% incidence. When the ≥5% limit is omitted, the most common TEAEs were hot flush and flushing (50,4%), hypertension and essential hypertension (15,3%), pain in extremity (9.5%) with possibly related TEAEs (bone pain 2.9%, musculoskeletal pain 2.9%, myalgia 0.7%), injection site pain (7.3%), arthralgia (6.6%), fatigue (6.6%) with related asthenia (3,6%), nocturia (5.8%) with possibly related TEAEs of micturition urgency (3,6%) and pollakiuria (1,5%), back pain (5.1%) and the possibly related TEAEs listed earlier (e.g. bone pain), and nasopharyngitis (5.1%) with possibly related TEAEs (localised infection 1,5% and sinusitis 4,4%). Slight differences for the percentages are noted in the two most common AEs (flushing and hypertension), which is related to differences in categorisation. Thus, the spectrum of TEAEs is in general the same with and without the 5% limit.

Table 19. Incidence of TEAEs ≧ 5% by PT in Study FP01C-13-001

	Part I (N = 33)			Part II (N = 104)			Total (N = 137)		
Preferred Term	Event	Subject	(%)	Event	Subject	(%)	Event	Subject	(%)
Hot flush	18	18	(54.5%)	51	49	(47.1%)	69	67	(48.9%)
Hypertension	2	2	(6.1%)	21	18	(17.3%)	23	20	(14.6%)
Pain in extremity	3	2	(6.1%)	15	11	(10.6%)	18	13	(9.5%)
Injection site pain	6	5	(15.2%)	7	5	(4.8%)	13	10	(7.3%)
Arthralgia	5	4	(12.1%)	7	5	(4.8%)	12	9	(6.6%)
Fatigue	3	3	(9.1%)	7	6	(5.8%)	10	9	(6.6%)
Nocturia	1	1	(3.0%)	8	7	(6.7%)	9	8	(5.8%)
Back pain	4	4	(12.1%)	3	3	(2.9%)	7	7	(5.1%)
Nasopharyngitis	4	4	(12.1%)	5	3	(2.9%)	9	7	(5.1%)

The MedDRA version was 19.1.
The AE percentage: 100%*The number of subjects with event (n) / Total number of subjects in Safety population (N) For subject with the same AE but multiple different severity/relationship (which resolution date=onset date or resolution date=onset date+1, except they had different AE No.), the multiple events would be combined as one AE with the maximum severity/relationship category for analysis.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.

Initially 15 events of QTcF increases in nine patients were identified in the main study, none in the extension study. The applicant included a separate ECG report in which measurements of ECGs and case re-evaluations were made by a cardiologist. In nine of the 15 events alternate explanations for QT prolongation were present (QT prolonged at baseline/screening, a QT prolonging drug newly added or ventricular pacing). Thus, six QT prolongation events could be associated to leuprolide treatment. Five of these were eliminated by ECG re-measurement. Of note, re-assessments were performed only on cases with QTc prolongation.

The most common TEAEs that became more frequent during the safety extension period compared with the main study were acute kidney injury, blood triglycerides increased, dehydration, dizziness, fall, and fatigue (Table 20). These occurred in 2 patients each (6.67%). In total, acute kidney injury occurred in 3/137 (2,2%) of the patients in FP01C-13-001 and in 2/30 in extension study (6.7%), which is more frequent than usually seen in relation to ADT use (e.g., about 5/1000 in Lapi et al. 201312; no mention in the Eligard SmPC).

The AEs that remained the most prominent during the extension period were hypertension and dizziness.

Only one drug related AE, a moderate neutropenia, was reported during FP01C-13-001-EX. However, neutropenia is not a listed reaction to leuprorelin-containing medicinal products for injection. The last dose of LMIS for this patient was given 5.5 months before the neutropenia occurred and the patient was using clopidrogel which has neutropenia as a rare ADR. Thus, no safety signal arose from this case.

[12] Lapi F, Azoulay L, Niazi MT, Yin H, Benayoun S, Suissa S. Androgen Deprivation Therapy and Risk of Acute Kidney Injury in Patients With Prostate Cancer. JAMA 2013;310(3):289-96.

Table 20. Incidence of newly occurring TEAEs in Study FP01C-13-001-EX

	Previous TEAEs (N=137)			New TEAEs (N=30)			Total TEAEs (N=137)		
Preferred Term	**Event**	**Subject**	**(%)**	**Event**	**Subject**	**(%)**	**Event**	**Subject**	**(%)**
Acute kidney injury	3	3	(2.19%)	2	2	(6.67%)	5	5	(3.65%)
Blood triglycerides increased	0	0	(0%)	2	2	(6.67%)	2	2	(1.46%)
Dehydration	1	1	(0.73%)	3	2	(6.67%)	4	3	(2.19%)
Dizziness	5	5	(3.65%)	2	2	(6.67%)	7	6	(4.38%)
Fall	7	3	(2.19%)	2	2	(6.67%)	9	5	(3.65%)
Fatigue	10	9	(6.57%)	2	2	(6.67%)	12	11	(8.03%)
Hypertension	23	20	(14.60%)	2	2	(6.67%)	25	22	(16.06%)

Previous TEAEs: The TEAEs were captured from previous FP01C-13-001 study; New TEAEs: The TEAEs were captured from FP01C-13-001-EX study; Total TEAEs: The combination of previous TEAEs and New TEAEs.
The N indicated the number of safety population, defined as subjects receiving at least one dose of LMIS 50 mg.
The MedDRA version was 20.1.
The AE percentage: 100%*the number of subjects with event (n) / Total number of subjects in Safety population (N)
For subject with the same AE but multiple different severity/relationship (which resolution date=onset date or resolution date=onset date+1, except they had different AE No.), the multiple events would be combined as one AE with the maximum severity/relationship category for analysis.
AE = adverse event; LMIS = leuprorelin mesilate injectable suspension; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event

2.6.8.3. Serious adverse event/deaths/other significant events

In Study FP01C-13-001, SAEs occurred in 20 patients (14.6%) and the most common SAE was subdural haematoma in two patients (1.5%) (Table 21). Only three SAEs were drug-related: blurred vision, left hip fracture, and myocardial infarction.

Concerning cardiac disorders, there were four SAEs in three patients (angina pectoris 2, myocardial infarction 1, atrial fibrillation 1), not deemed related to LMIS.

Altogether four fractures were reported, three in the main study and one in the extension study, in three patients. Thus, the frequencies of fractures as 3/137 (2,2%) and 1/30 (3,3%) are in line with those detected in ADT treated men with prostate cancer (e.g., SmPC for Eligard).

During the safety extension period, there were seven new SAEs reported in four patients. None was related to LMIS 50 mg. No deaths occurred during the extension study.

In the literature-based data, cardiac events were highlighted among the SAEs. These occurred, however, often in patients with medical history of significant risk factors. In total, 26 deaths were reported in two publications with no details from 25 cases.

For the SAEs and deaths identified in the FAERS database: See section "Published literature and databases".

Table 21. Summary of incidence of SAEs in Study FP01C-13-001 and the safety extension

	Previous SAEs (N = 137)			New SAEs (N = 30)			Total SAEs (N = 137)		
	Event	Subject	(%)	Event	Subject	(%)	Event	Subject	(%)
OVERALL	34	20	(14.60%)	7	4	(13.33%)	41	22	(16.06%)
Subdural haematoma	2	2	(1.46%)	0	0	(0%)	2	2	(1.46%)
Acute respiratory failure	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Angina pectoris	2	1	(0.73%)	0	0	(0%)	2	1	(0.73%)
Asthenia	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Asthma	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Atrial fibrillation	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Bronchitis bacterial	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Cerebrovascular accident	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Chronic obstructive pulmonary disease	3	1	(0.73%)	0	0	(0%)	3	1	(0.73%)
Clostridium difficile colitis	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Colon adenoma	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Colon cancer	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Death	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Deep vein thrombosis	0	0	(0%)	1	1	(3.33%)	1	1	(0.73%)
Dehydration	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Diabetic foot	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Dysphagia	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Dyspnoea	0	0	(0%)	1	1	(3.33%)	1	1	(0.73%)
Hip fracture	1	1	(0.73%)	1	1	(3.33%)	2	1	(0.73%)
Intermittent claudication	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Joint dislocation	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Knee arthroplasty	0	0	(0%)	1	1	(3.33%)	1	1	(0.73%)
Metabolic encephalopathy	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Myocardial infarction	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Non-cardiac chest pain	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Osteoarthritis	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Perforated ulcer	0	0	(0%)	1	1	(3.33%)	1	1	(0.73%)
Peripheral artery occlusion	2	1	(0.73%)	0	0	(0%)	2	1	(0.73%)
Pneumonia	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Pneumothorax spontaneous	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Prostate cancer metastatic	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Pyelonephritis acute	0	0	(0%)	1	1	(3.33%)	1	1	(0.73%)
Sepsis	0	0	(0%)	1	1	(3.33%)	1	1	(0.73%)
Vertigo	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Vision blurred	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)

Previous SAEs: The SAEs were captured from previous FP01C-13-001 study; New SAEs: The SAEs were captured from FP01C-13-001-EX study; Total SAEs: The combination of previous SAEs and New SAEs.

The N indicated the number of safety population, defined as subjects receiving at least one dose of LMIS 50 mg.

The MedDRA version was 20.1.

The AE percentage: 100%*the number of subjects with event (n) / Total number of subjects in Safety population (N)

For subject with the same AE but multiple different severity/relationship (which resolution date=onset date or resolution date=onset date+1, except they had different AE No.), the multiple events would be combined as one AE with the maximum severity/relationship category for analysis.

AE = adverse event; LMIS = leuprorelin mesilate injectable suspension; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event

2.6.8.4. Laboratory findings

Haematology

In the main study, clinically significant changes in biochemical parameters were reported in three patients. None of these findings was found to be related to the dosing of LMIS 50 mg. During the safety extension, one patient had a clinically significant case of lower than normal neutrophil counts that was possibly related to study drug, and two patients had clinically significant abnormalities in biochemical assessment. In the literature, anaemia, including serious cases, was reported as AEs of interest and with incidence "common" (the frequency mentioned also in the proposed SmPC) although, only two of the anaemia AEs were considered treatment-related. In study FP01C-13-001 no cases of anaemia were reported.

Blood Chemistry

Three patients had clinically significant increases in blood glucose levels: two in the main study and one in the safety extension. One normalised by the end of the study and the other patients had pre-existing conditions (diabetes and hypercholesterolaemia). History or presence of Type I or Type II diabetes mellitus (unless only oral hypoglycaemic required) were criteria for exclusion, which let advanced diabetes mellitus with several oral antidiabetic drugs in their regimen to enter the study. In Study FP01C-13-001, there were AEs related to diabetes mellitus including a severe case of diabetic foot (a long-term complication of diabetes mellitus). HgbA1c was monitored during the safety extension period only. This information is reflected in the SmPC: "Hyperglycaemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Hyperglycaemia may represent development of diabetes mellitus or worsening of glycaemic control in patients with diabetes. Monitor blood glucose and/or HgbA1c periodically in patients receiving a GnRH agonist and manage with current practice for treatment of hyperglycaemia or diabetes".

2.6.8.5. Safety in special populations

The PK of LMIS 50 mg in subjects with renal or hepatic impairment has not been investigated.

Camcevi 42 mg is contraindicated in women and paediatric patients.

Safety data for patients older (≥ 75 years) were submitted during the procedure: As the main trial had no upper limit for age, the trial had a fairly large proportion of aged patients of ≥75 years of age (37,2%). The overall incidence of TEAEs was 68,6% in <65 years (overall population in this age group 35 patients), 84,3% in 65-74 years (51 patients), 91,1% in 75-84 years (45 patients) and 100% in >84 years (six patients).

In general, the spectrum of the most frequent AEs in aged patients did not significantly differ from those detected in younger patients. Furthermore, some detected differences may be related to the small number of patients. Regarding AEs of special interest, only fatigue increased systematically with growing age

In the main study and its extension there were no patients with bodyweight <40 kg. 17 patients weighed more than 100 kg in these studies. In these patients with the 10% cut-off the most common

TEAEs were hot flush (58.8%), followed by hypertension (23.5%), back pain (11.8%), fatigue (11.8%), and nocturia (11.8%). Here the small number of patients and the cut-off of 10% can be partly related to differences in TEAE frequencies when compared to the whole study population.

2.6.8.6. Immunological events

No information available which is acceptable.

2.6.8.7. Safety related to drug-drug interactions and other interactions

NO new drug-drug interaction studies were provided which is acceptable.

2.6.8.8. Discontinuation due to adverse events

There were 15 (10.9%) discontinued subjects. Of the 15 discontinued subjects 5 subjects (5/137, 3.6%) discontinued the study due to experiencing the following adverse events: acute kidney injury, atrial fibrillation, cerebrovascular accident, death, hormone-refractory prostate cancer, and metastatic prostate cancer.

Published literature and databases

To complement this application publications from other trials and FAERS data were included.

A PubMed search for years 1986-2019 was run and re-run as of October 2020. Initial search included the terms "leuprolide" or "leuprorelin", "6 month", "study" and was then narrowed down to restrict to "prostate". The re-run omitted the term leuprolide as it did not provide additional hits. Publication language was restricted to English. The initial search resulted in more than 180 hits and the re-run in 207 hits. Major new publications suitable for comparison with the main study FP01C-13-001 were not identified.

The FAERS data presented in the submitted material are from the year 2017 only. According to the applicant, the rational for this approach was to capture AEs not included in the most recent labelling updates. In this MAA, Eligard SmPC from year 2019 is used.

The applicant described that technically "leuprorelin or Lupron or Eligard" was used as the keyword for "DRUGNAME" with the option "ps" (primary suspect) picked. This would exclude events where there are several drugs involved in the causality and where leuprorelin is included but not as the primary suspect (e.g. drug-drug interactions with substrates known to prolong QT interval).

The most common AE presented originating from the FAERS data was death. For the period concerned (Q1/2017 through Q4/2017), 'death' is listed as the most commonly reported AE (190 events, corresponding to an event frequency of 14.8% based on total number of events reported). When cases with a reported outcome of death were collected, the overall cases of death amounted to 302 deaths, corresponding to a frequency of 23.5% based on total number of cases reported. However, prostate cancer is serious disease and the cases identified in FAERS data were subjects of at least 60 years of age. Thus, these events can be related to e.g. progression of metastatic prostate cancer or to causes related to comorbidities in this aged population.

Many of the most common AE types related to leuprorelin use in the FAERS data are about the technical issues with the existing products. The use of prefilled syringe suggested for Camcevi was

created to address this medical need. With a pre-filled syringe medication errors are expected to be rarer.

Otherwise (despite deaths and medication errors) the reported AEs do not differ remarkably from those presented for FP01C-13-001.

Findings from the Eudravigilance data from January 2017 to September 2020 were provided. Mirroring to the total number of cases in EEA sources (n=4966), e.g. the frequency of fatal AEs (n=1140) as 22,9% is comparable to FAERS data from 2017. Divided by the year of EudraVigilance gateway receipt the proportion of deaths as the fatal AE has increased from 54,1% (2017) to 73,5% (2020 up to end of September). However, the total number of different fatal AEs varies by each year and does not show a growing trend. Almost all were spontaneous reports and a majority were unconfirmed and did not contain additional details. Similarly, the total number of non-fatal but serious AEs varies by each year and does not show a growing trend.

Post marketing experience

LMIS 50 mg has not been approved or marketed anywhere in the world, nor has it been withdrawn from marketing / registration in any country.

2.6.9. Discussion on clinical safety

Leuprorelin has been on the EU market for more than 30 years, and the reference product Eligard 45 mg for more than 10 years. LMIS 50 mg formulation contains NMP as an excipient. As the dose of NMP is of the same order of magnitude (139.40 mg of NMP in LMIS 50 mg and 165 mg of NMP in Eligard) of Eligard and the dosing interval is the same (once in 6 months), this is considered acceptable.

The applicant has submitted data from a new Phase 3 trial (FP01C-13-001) with a safety extension (FP01C-13-001-EX). In addition, two PK analyses were performed. Complementarily, publications from PubMed up to October 2020 and FAERS data have been submitted. In addition, the applicant provided EU data originating from EudraVigilance from January 2017 to September 2020.

In Study FP01C-13-001, 137 patients were exposed to LMIS 50 mg and 128 patients received the planned two doses. The safety findings of the PK analyses performed by the applicant are included in FP01C-13-001 safety data. Healthy volunteers have been mentioned in relation to one publication

Study FP01C-13-001 began with the intention of enrolling 30 patients for frequent safety monitoring (Part I). In addition, the first 10 patients were under more frequent monitoring of safety endpoints. Eventually, 33 prostate cancer patients were enrolled in Part I. Of these 12% did not complete the study when the proportion of not completing the study was 11% in the whole 137 patient population.

To evaluate whether the risk for post-dose AEs is related to higher serum concentrations of leuprolide mesilate, the graphs plotting the individual time-concentration profiles for the first three days after dosing with the time of any AEs occurring for each individual during this time period were presented (data not shown). No direct association between serum concentration and timing of AEs was detected.

In FP01C-13-001, most common TEAEs were hot flush (48.9%), 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%) (by PT and with ≥5% incidence). When the 5% limit is omitted the spectrum of the TEAEs is similar and the spectrum of TEAEs is typical to the applied treatment and to the treated patient population.

The most common TEAEs that became more frequent during the safety extension period compared with the main study were acute kidney injury, blood triglycerides increased, dehydration, dizziness, fall, and fatigue. These occurred in two patients each. In total, acute kidney injury occurred in in 3/137 (2,2%) patients in the main study and in 2/30 in extension study (6.7%), which is much more than usually seen in relation to ADT use. However, these were not regarded as drug-related and the patients had clear risk factors for renal failure. The AEs that remained the most prominent during the extension period were hypertension and dizziness. Only one drug related AE, a moderate neutropenia, was reported during FP01C-13-001-EX. The mention about leuprorelin having minor influence on the ability to drive and use machines in the proposed SmPC section 4.7 is endorsed.

Hypertension was a relatively frequent TEAE in the main study and in its extension. However, the applicant's justifications with reference to Eudravigilance and published data for not upgrading this from uncommon to common ADR in SmPC are supported. Also the cardiac SAEs (four in three patients) in the main study have other plausible background factors. Furthermore, the suggested SmPC includes an overarching warning for cardiovascular diseases in 4.4., along the lines of Eligard.

SAEs occurred in 20 patients (14.6%) and the most common SAE was subdural hematoma (1.5%, two patients) in Study FP01C-13-001. Only three SAEs were drug-related: blurred vision, left hip fracture, and myocardial infarction. The narratives of these cases contain only limited information. No detailed information about the SAEs are given, *e.g.*, whether the myocardial infarction was related to QT prolongation. Altogether four fractures were reported, three in the main study and one in the extension study, in three patients. Thus the frequencies of fractures as 3/137 (2,2%) and 1/30 (3,3%) are in line with those detected in ADT treated men with prostate cancer (e.g., SmPC for Eligard).

Of three deaths in the main trial none was related to the use of LMIS 50 mg. During the safety extension period, there were seven new SAEs reported in four patients. None of these SAEs was related to LMIS 50 mg. A case of blurred vision was concomitantly diagnosed with a cataract and hyperopia. However, impaired vision is a listed reaction for leuprorelin-containing medicinal products for injection and relationship between LMIS 50 mg is possible. No deaths occurred during the extension study. In the literature-based data, cardiac events were highlighted among the SAEs. These occurred, however, often in patients with medical history of significant risk factors.

In the main study, only few clinically significant changes in biochemical parameters were reported, and none of these were found to be related to the dosing of LMIS 50 mg. During the safety extension, one patient had a clinically significant case of lower than normal neutrophil counts that was possibly related to study drug, and two patients had clinically significant abnormalities in biochemical assessment. In the literature, anaemia, including serious cases, was reported with incidence "common" (the frequency mentioned also in the SmPC). This differs from FP01C-13-001 where no cases of anaemia were reported. However, only two of the anaemia AEs in the literature were considered treatment-related.

Clinically significant changes in ECG recordings were reported. It is known that spontaneous and induced hypotestosteronaemia is associated with an increase in QTc. Overall, nine patients had 15 outlier QTcF responses: QTcF $\geq$ 500 msec, or QTcF $\geq$ 480 msec with dQTcF $\geq$ 60 msec, or both. Leuprorelin treatment was initially regarded as the probable cause of QT prolongation in five patients. However, after a post hoc ECG analysis, only 1 case of QT prolongation was ascribed to leuprorelin therapy. The proposed SmPC section 4.4 warns about QT prolongation in patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval. The SmPC text is complemented with "Periodic monitoring of electrocardiograms and electrolytes should be considered" which is endorsed.

Update of the frequency of QT prolongation from "not known" to "uncommon" is included in the SmPC's 4.8. ADT table.

Drug-drug interactions known to prolong QT interval or to induce *Torsade de pointes* are adequately described in the proposed SmPC (in line with the reference product).

Reported local skin reactions to the injection were mild or moderate in severity and were resolved by the end of study.

In patients receiving a GnRH agonist, blood glucose and/or HgbA1c should be monitored periodically. This issue is handled in the SmPC, which is acceptable. HgbA1c was monitored during the safety extension period only. History or presence of Type I or Type II diabetes mellitus (unless only oral hypoglycaemic required) were criteria for exclusion, which let patients with advanced diabetes mellitus with several oral antidiabetic drugs in their regimen to enter the study. It is notable that in Study FP01C-13-001, there were AEs related to diabetes mellitus including a severe case of diabetic foot (a long-term complication of diabetes mellitus).

According to the proposed SmPC, contraindications include patients who previously underwent orchiectomy, and as sole treatment in patients with spinal cord compression or evidence of spinal metastases. In addition, LMIS 50 mg is proposed to be contraindicated in women and paediatric patients.

The intended indication is prostate cancer, thus no between-gender differences (AEs in women) or risk of adverse pregnancy outcomes are applicable, neither are the AEs in paediatric population. The SmPC's section 4.6 "Fertility, pregnancy and lactation" has been updated to reflect that "Camcevi is contraindicated in women. Based on findings in animals and mechanism of action, leuprorelin may impair fertility in males of reproductive potential (see section 5.3)."

As the main trial had no upper limit for age, it can be expected that with rising age also the frequency of AEs rises as the comorbidity burden typically increases. In general, the spectrum of the most frequent AEs in aged patients did not significantly differ from what was detected in younger patients. Furthermore, some detected differences may be related to the small number of patients. Regarding AEs of special interest, only fatigue increased systematically with growing age. The body weight typically decreases with growing age. However, it is not known whether this is related to the AEs seen. Leuprorelin concentrations increase with age but are still within the therapeutic dose range. These findings do not indicate any new safety concerns.

Safety data in patients with renal impairment / renal failure and in patients with hepatic impairment were provided. For renal function data for BUN, serum creatinine and estimated CrCl values was provided for 5 patients who developed renal impairment during the study. No new safety concerns emerged from these. The applicant also reported in FP01C-13-001 and FP01C-13-001-EX studies 3 AEs of hepatic disorder and 5 patients with abnormalities in ALT and AST levels, all < 8 x UL. These did not raise new safety concerns.

Common role of acute kidney injuries, dehydration, dizziness, falls, and fatigue not only as separate events but as a phenomenon where the clustering of these different AE types may be in relation to each other (in the whole safety population and separately in different special populations, *e.g.*, elderly) were presented but no obvious interactions could be detected from the different TEAEs (acute kidney injury, dizziness, dehydration, falls, fatigue). The low number of patients with very high age together with low number of some of the events precluded firm conclusions.

In the main study and its extension there were no patients with bodyweight <40 kg. 17 patients weighed more than 100 kg in these studies. In these patients with the 10% cut-off the most common TEAEs were hot flush (58.8%), followed by hypertension (23.5%), back pain (11.8%), fatigue (11.8%), and nocturia (11.8%). Here the small number of patients and the cut-off of 10% can be partly related to differences in TEAE frequencies when compared to the whole study population.

Generally, the co-medications and presumed comorbidities are in line with what would be expected for this population.

According to current scientific knowledge, this peptide does not raise immunological safety concerns.

In relation to the amount of patients experiencing AEs (83.2%), the amount of patients discontinuing the study (3.6%) was low implying relatively good tolerability.

LMIS 50 mg has not been approved or marketed anywhere. Concerning other marketed leuprorelin products, the presented post-marketing data were scarce. The FAERS data presented contains voluntary reports from populations of uncertain size, and thus it is difficult to reliably estimate the frequency or establish a causal relationship to drug exposure. For the period concerned (Q1/2017 through Q4/2017), 'death' is listed as the most commonly reported AE (190 events, corresponding to an event frequency of 14.8% based on total number of events reported). When cases with a reported outcome as death were collected, the overall cases of death amounted to 302 deaths, corresponding to a frequency of 23.5% based on total number of cases reported. However, prostate cancer is serious disease and the cases identified in FAERS data were subjects of at least 60 years of age. Thus, these events can be related to e.g. progression of metastatic prostate cancer or to causes related to comorbidities in this aged population.

Eudravigilance data from January 2017 to September 2020 (n=4966) showed e.g. the frequency of fatal AEs (n=1140) as 22,9% which is comparable to FAERS data from 2017. For death as the most common AE it is difficult to draw conclusions regarding the role of leuprorelin treatment, due to the limited amount of case details. As prostate cancer is a serious disease the most plausible explanation in fatal cases could be disease progression in metastatic stage and also the typical comorbidity burden these patients tend to have. Divided by the year of EudraVigilance gateway receipt, the proportion of deaths as the fatal AE has increased from 54,1% (20117) to 73,5% (2020 up to end of September). However, the total number of fatal AEs varies by each year and does not show a growing trend. From the 721 cases reported as death in the fatal AEs, one MAH has reported 95% of them, almost all were spontaneous reports and a majority were unconfirmed and did not contain additional details. Similarly, the total number of non-fatal but serious AEs varies by each year and does not show a growing trend. The spectrum of these AEs is as expected and mirrors the findings in the main study and clinical experience. On the whole, the retrieved data did not give rise to previously unknown safety concerns.

Results from a comprehensive literature search including Phase 4 studies about post-marketing safety of 6-month leuprorelin depot forms using PubMed and Google Scholar with a search up to October 202 were presented with the search string Leuprolide/Leuprorelin AND English AND Clinical Trial, Phase IV. However, no publications were found, nor by adding 'post marketing'. Adding "Case reports", 461 publications were retrieved. The applicant did not bundle these into main themes but presented some examples (e.g. pituitary apoplexy, convulsions and interstitial lung disease, which are included in the proposed SmPC for Camcevi). The contents of these case reports are likely to be highly variable and also mirror the high prevalence of prostate cancer. Based on the long clinical use of leuprorelin products and the cases presented no additional measures are suggested.

2.6.10. Conclusions on the clinical safety

The application is based mainly on data from one Phase 3 trial. The AEs were mostly in line with the previous experience with leuprorelin products. The medication errors may be less frequent with this new product, but class type effects, such as risk of QT prolongation, remain as safety concerns to be closely monitored.

To strengthen the application the applicant has provided additional findings from published literature and from FAERS and Eudravigilance Data. These do not give rise to new safety issues.

2.1. Risk Management Plan

2.1.1. Safety concerns

None.

2.1.2. Pharmacovigilance plan

Not applicable.

2.1.3. Risk minimisation measures

Not applicable.

2.1.4. Conclusion

The CHMP considers that the risk management plan version 0.3 is acceptable.

2.2. Pharmacovigilance

2.2.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.2.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.3. Product information

2.3.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Camcevi is indicated for the treatment of hormone-dependent advanced prostate cancer and for the treatment of high-risk localised and locally advanced hormone-dependent prostate cancer in combination with radiotherapy.

3.1.2. Available therapies and unmet medical need

This marketing authorisation application is for a leuprorelin mesilate injectable suspension (LMIS) 50 mg, containing leuprorelin mesilate equivalent to 42 mg leuprorelin (Camcevi 42 mg), supplied as ready-to-use drug product in contrast to the available products requiring pre-mixing prior subcutaneous injection.

LMIS 50 mg is the first ready-to-use leuprorelin prolonged-release pharmaceutical form for 6-month dosing intervals. The product was developed to address the respective medical need in leuprorelin-based androgen deprivation therapy (ADT) as handling errors with depot formulations were frequently reported leading to the ongoing referral procedure (refer to EMA/316598/2019).

Camcevi does not provide a novel therapeutic approach nor address an unmet medical need. In this indication several other pharmaceutical products are available, e.g., other leuprorelin formulations, triptorelin, goserelin, which are also endorsed by several international therapeutic guidelines.

3.1.3. Main clinical studies

The clinical study supporting this application for LMIS 50 mg is the Phase 3 study FP01C-13-001, which is a completed, uncontrolled, multicentre, open-label, single-arm, 12-month, two-part PK, safety and PD/efficacy study conducted in 137 males with prostate carcinoma in need of androgen deprivation therapy.

3.2. Favourable effects

Leuprorelin has been on the EU market for more than 30 years, and the reference product Eligard 45 mg for more than 10 years.

In the LMIS 50 mg clinical study, the percentage of subjects with a serum testosterone of ≤50 ng/dL (castrate level) by Day 28 was 98.5% (135/137 subjects) in the ITT population and 99.2% (123/124 subjects) in the PP population. The percentage of subjects with testosterone suppression from Day 28 through Day 336 was 97.0% (133/137 subjects) in the ITT population and 97.6% (121/124 subjects) in the PP population. Thus, the primary efficacy endpoint of serum testosterone concentration suppression below castrate level was met and was comparable to those of the reference product Eligard 50 mg and the results in published literature.

The percentage of subjects with a more stringent serum testosterone level ≤20 ng/dL by Day 28 was 70.4% (95/135) in the ITT population. On Day 336, of the subjects who completed the study, 95.9% (117/122) achieved serum testosterone level <20 ng/dL. Regarding the more stringent castration

level, the serum testosterone concentration suppression was comparable to the results in the published literature.

The serum PSA levels decreased along the two doses of LMIS 50 mg until the end of the study in majority of the cases in both ITT and PP Populations (at baseline median 8.3 ng/mL, range 0.06-2748.4 and at end of study (EOS) median 0.23 ng/mL, range 0.06-633.5 in the ITT population).

The serum LH levels followed the known course of acute and transient increase after the first dose of LMIS 50 mg decreasing thereafter below the baseline except for the slight and transient increase after the second dose decreasing thereafter to low level until the EOS.

3.3. Uncertainties and limitations about favourable effects

No comparative studies or bioequivalence studies have been performed, and only published data on Eligard 50 mg is used as a reference.

The clinical characteristics of patients included in the clinical studies for LMIS 50 mg and Eligard 45 mg differ to some extent from each other e.g., by stage distribution, even though the inclusion criteria were relatively similar. However, this is not expected to hamper the assessment of the primary endpoint, i.e., the testosterone suppression, but may have influence on secondary endpoints, e.g., PSA levels.

The PSA recurrence was reported in a subset of patients with slight to significant increases of mean PSA levels towards the end of the study. Due to lack of information (PSA values) it is not possible to deem how many patients actually developed castration resistant disease during the study.

Median serum testosterone concentration-time profiles were lower in Asian subjects compared to non-Asian subjects. However, there were only five Asian patients, and no conclusions based on these few patients can be drawn.

The efficacy (and safety) data in patients with renal impairment/insufficiency and treated with LMIS 50 mg is very limited.

3.4. Unfavourable effects

In the main FP01C-13-001 study, the AEs were reported at a rate consistent with those reported in the labelling of Eligard 45 mg (SmPC Eligard, 2019) and in the published literature: the most common TEAEs were hot flush (48.9%), 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%), and the most common drug related AEs were hot flush (48.2%), injection site pain (7.3%) and fatigue (5.8%). Reported local skin reactions to the injection were mild or moderate in severity and were resolved by the end of study. The most common drug-related AEs were hot flush, injection site pain, and fatigue. With regard to the severity of reported AEs, most AEs were mild or moderate.

The most common TEAEs that became more frequent during the safety extension period compared with the main study were acute kidney injury, blood triglycerides increased, dehydration, dizziness, fall, and fatigue, which occurred in two patients each (6.67%). The AEs that remained the most prominent during the extension period were hypertension and dizziness.

In addition, acute kidney injury was seen in 2.19% and 6.67% in Studies FP01C-13-001 and FP01C-13-001-EX, respectively.

Overall, nine patients had 15 outlier QTcF responses (QTcF ≥ 500 msec, or QTcF ≥ 480 msec with dQTcF ≥ 60 msec, or both); leuprorelin treatment was initially regarded as the probable cause in five patients. However, after reanalysis only 1 case was ascribed to leuprorelin therapy.

SAEs occurred in 20 patients (14.6%), and no more than three of the SAEs were drug-related. In addition, there were three deaths of which none was drug-related. No deaths occurred during the extension study.

Treatment was discontinued in 10.9% of subjects. Of the discontinued subjects 3.6% discontinued the study due to adverse events.

In the literature-based data, cardiac events were highlighted among the SAEs.

3.5. Uncertainties and limitations about unfavourable effects

No comparative PD/efficacy/safety studies were performed with LMIS 50 mg, which hampers assessments. The study population was rather heterogeneous regarding previous medical histories, prostate cancer disease extent, previous anticancer therapies and regarding prostate cancer trajectory. Due to limited study size, definitive conclusions about safety findings in special populations are difficult to make. However, taking into account the long clinical use of leuprorelin products, these issues will not be pursued further.

The safety data in patients with renal impairment/insufficiency and treated with LMIS 50 mg is very limited.

The higher than expected number of acute kidney injury cases can be related to enrolment of patients with risk factors for renal failure. However, these were not regarded as drug-related.

No cases of anaemia were reported in the main study, although in the literature, anaemia, including serious cases, was reported with incidence "common". The narratives of the SAEs contain only limited information.

No safety data is available on the use of Camcevi when used in association with prostatic irradiation, as prostatic radiotherapy was listed among contraindications. Further, no data on administration errors when compared to other formulations of Leuprorelin were provided.

3.6. Effects Table

Table 22. Effects table for LMIS 50mg in the treatment of hormone-sensitive prostate cancer in FP01C 13 001 (data cut-off: 02-Sep-2016).

Effect	Short Description	Unit	Camcevi	No Control	Uncertainties/ Strength of evidence
Favourable effects					
Serum testosterone level decrease below castrate level <50 ng/dL*	By Day 28 From D 28 through D 336	%	98.5% ITT 99.2% PP 97.0% ITT 97.6% PP	N/A	Post-suppression excursions after the second dose
Serum testosterone level decrease below castrate level <20 ng/dL	By Day 28 From D 28 through D 336	%	70.4% ITT 95.9% PP	N/A	A stricter castrate level has been associated with better prognosis.

Effect	Short Description	Unit	Camcevi	No Control	Uncertainties/ Strength of evidence
Serum PSA level (clinical benefit)	At baseline By D 336	ng/ dL	Median 8.3 (0.06-2748) ITT Median 0.23 (0.06-633.5) ITT	N/A	The PSA recurrence
Serum LH level (suppression)	At baseline By D 336	IU/L	Median 6.8 (2.20-48.61) ITT¤ Median 0.09 (0.07-1.0) ITT¤	N/A	The increase of the serum LH levels towards the EOS
Unfavourable effects					
TEAEs	total	%	83.2	N/A	Excluding safety extension period (FP01C 13 001 EX)
- Hot flush	total	%	48.9	N/A	
- Hypertension	total	%	14.6	N/A	
- Pain in extremity	total	%	9.5	N/A	
- Injection site pain	total	%	7.3	N/A	
Drug-related Aes	total	%	62.0	N/A	Excluding safety extension period (FP01C 13 001 EX)
SAEs	total	%	14.6	N/A	Excluding safety extension period (FP01C 13 001 EX)
Deaths	total	%	2.2	N/A	(No deaths in FP01C 13 001 EX)
Aes leading to discontinuation	total	%	3.6	N/A	(No AE led to discontinuation in FP01C 13 001 EX)

Abbreviations: ITT= ITT population, PP= PP population
* Primary efficacy endpoint
¤ PRL Lab

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The clinical benefit of the new leuprorelin mesilate formulation is the new simpler method of administration. The active substance leuprorelin mesilate has the same therapeutic targets as all leuprorelin acetate formulations already on market.

A single-arm clinical study (FP01C-13-001) was conducted with LMIS 50 mg for evaluation of the PK, PD, efficacy, and safety. No bioequivalence study was conducted.

The essential bridge demonstrating that the effect of LMIS 50 mg on the biological markers (i.e., suppression of testosterone levels testosterone, LH and PSA), typical of ADT was similar to that described in the published literature/clinical studies on Eligard45 mg has been made. The bridging was supported by the non-clinical and clinical pharmacokinetic findings.

The *in vitro* release data can only be considered as supportive for the bridge due to the complex formulation of the products.

Concomitant treatment with radiation therapy other than for pain control was not allowed. Such design choices limit inference on relative efficacy, safety or commodity of Camcevi when compared to other commercially available formulations of leuprorelin.

Easy administration of the depot injection can be of help in avoiding medication errors (probably mainly leading to insufficient dosages). However, the absence of comparative data limits the safety inference for LMIS 50 mg in particular on-site administration-related adverse events and administration errors. Yet, as was verified in the trial. no difference will be expected on the adverse event profile attributable to the imposed modification of the hormonal milieu of patients.

3.7.2. Balance of benefits and risks

This hybrid application for LMIS 50 mg is based on bridging to the reference product (EU) Eligard 45 mg.

The PK simulations indicate that use of LMIS 50 does not result in intolerable exposures or peak concentrations. The PK-profile of LMIS 50 mg seems comparable with the referenced leuprorelin depot formulations. In the clinical study of LMIS 50, the efficacy endpoints (the biomarkers indicating successful ADT) have been met.

The safety profile seems comparable to the RefMP and with published literature. Some class effects, such as QT prolongation remain as safety issues to be monitored. No entirely new safety concerns have been identified.

The bridge built between the reference product EU-Eligard 45 mg and LMIS 50 mg to allow reference to the originator's pre-clinical and clinical data has been deemed acceptable.

Based on information provided it can be summarised that the administration of LMIS 50 mg resulted in suppression of testosterone below the castrate levels. The pharmacodynamic results obtained with LMIS 50 mg were comparable to those obtained by Eligard 45 mg.

The provided real-time *in vitro* release data can only be considered as supportive for the bridge between LMIS 50 mg and the reference medicinal product EU-Eligard 45 mg due the complex formulation of the products; the serum concentrations of leuprorelin were similar after s.c. administration of LMIS 50 mg (#FP01C-13-001) and Eligard 45 mg (published data for #AGL-0205), which is considered as supportive data for the bridge.

In conclusion, bridging has been sufficiently demonstrated based on the pharmacodynamic responses of testosterone suppression, supported by *in vitro* release characteristics, non-clinical findings, and clinical pharmacokinetic findings.

Conclusions

The overall B/R of Leuprorelin mesilate 50 mg for the treatment for the treatment of hormone dependent advanced prostate cancer and for the treatment of high-risk localised and locally advanced hormone dependent prostate cancer in combination with radiotherapy is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Camcevi is favourable in the following indication(s):

CAMCEVI is indicated for the treatment of hormone dependent advanced prostate cancer and for the treatment of high-risk localised and locally advanced hormone dependent prostate cancer in combination with radiotherapy.

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.