Amsterdam, 26 February 2026
EMADOC-1700519818-2921322
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Camcevi

International non-proprietary name:Leuprorelin

Procedure No. EMA/X/0000258054

Note

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

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List of abbreviations

ADR	Adverse drug reaction
ADT	Androgen deprivation therapy
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BfArM	Germany's Federal Institute for Drugs and Medical Devices
CAPA	Corrective and preventive action
CAT	Committee for Advanced Therapies
CHMP	Committee for Medicinal Products for Human Use
CMA	Critical material attribute
Cmax	Maximum concentration
CPP	Critical process parameter
CQA	Critical quality attribute
CRPC	Castrate-resistant prostate cancer
CT	Computed tomography
CV	Coefficient of variation
DoE	Design of experiment
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EOS	End of study
EU	European Union
EU-Eligard	Eligard® that has marketing authorization in the EU
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GnRH	Gonadotropin releasing hormone
GnRHR	Gonadotropin-releasing hormone receptor
IM	Intramuscular(ly)
ITT	Intention-to-treat
IV	Inherent viscosity
IV	Intravenous(ly)
LH	Luteinizing hormone
LHRH	Luteinizing hormone releasing hormone
MA	Marketing authorisation
MAA	Marketing authorisation application
MAH	Marketing authorisation holder
MRI	Magnetic resonance imaging
NA	Not applicable

NDA	New Drug Application
PD	Pharmacodynamics
PET/CT	Positron emission tomography/computed tomography
PK	Pharmacokinetics
PLGA	Poly(D,L-lactide-co-glycolide)
PP	Per protocol
PRAC	Pharmacovigilance Risk Assessment Committee
PSA	Prostatic specific antigen
QbD	Quality by design
QD	Once daily
QoL	Quality of life
QTPP	Quality target product profile
Q6M	6-monthly
Q3M	3-monthly
RBC	Red blood cells
RMP	Risk management plan
RMS	Reference Member State
SAE	Serious adverse event
SAL	Sterility assurance level
SC	Subcutaneous(ly)
SD	Standard deviation
SmPC	Summary of product characteristics
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
US-Eligard	Eligard® that has marketing authorization in the US
VAS	Visual analogue scale
WBC	White blood cells

1. Administrative/regulatory information and recommendations on the procedure

1.1. Submission of the dossier

On 07/03/2025 Accord Healthcare S.L.U. submitted an extension of the marketing authorisation.

Extension application to add a new strength of 21 mg for Leuprorelin prolonged-release suspension for injection pre-filled syringe, for subcutaneous (SC) administration.

1.2. Legal basis and dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point(s) (c) - Extensions of marketing authorisations.

1.3. Scientific advice and protocol assistance

Not applicable.

1.4. Information on paediatrics

Not applicable

1.5. Information on orphan market exclusivity

Not applicable

1.5.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH 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.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur:	Johanna Lähteenvuo

The application was received by the EMA on	07 March 2025
The procedure started on	27 March 2025
The CHMP Rapporteur's first Assessment Report was received on	16 June 2025

The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on	20 June 2025
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	24 July 2025
The MAH submitted the responses to the CHMP consolidated List of Questions on	09 October 2025
The CHMP Rapporteur circulated the Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	10 November 2025
The CHMP agreed on a list of outstanding issues to be sent to the MAH on	11 December 2025
The MAH submitted the responses to the CHMP List of Outstanding Issues on	26 January 2026
The CHMP Rapporteur circulated the Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 February 2026
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 on	26 February 2026

1.7. CHMP outcome

1.7.1. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of the new strength of 21 mg of Camcevi (leuprorelin) prolonged-release suspension for injection pre-filled syringe, for subcutaneous (SC) administration is favourable in 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 CHMP therefore recommends the extension(s) of the marketing authorisation for Camcevi subject to the conditions described in the following sections.

1.7.2. Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

1.7.3. Other conditions and requirements of the marketing authorisation

1.7.3.1. 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.

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

1.7.4.1. 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.

2. Introduction

2.1. Therapeutic Context

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.[1,2,3,4,5]

Population-based screening of men aged between 55 and 69 years, using PSA testing, has been evaluated in randomised trials[6]. After a median follow-up of 16 years, the European screening trial demonstrated a 25% relative reduction in the risk of prostate cancer mortality. However, 570 men needed to be invited for screening and 18 patients needed to be treated to prevent one death from prostate cancer. Risk-adapted early detection of prostate cancer using a baseline PSA has been evaluated in retrospective cohort studies. Men with a PSA >1 ng/ml at 40 years or >2 ng/ml at 60 years are at increased risk of prostate cancer metastasis or death from prostate cancer.[7,8]

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.[8,9]

Epidemiology

Prostate cancer is the second most commonly diagnosed cancer in men, with an estimated 1.4 million diagnoses and 375,000 deaths worldwide in 2020.[10,11,12] In Europe, it is the most frequently diagnosed cancer in men and the third cancer-related cause of death in men.[13]

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 the 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

[1] ACS 2013, American Community Survey Data https://www.census.gov/programssurveys/acs/guidance/comparing-acs-data/2013.html
[2] Crocetti E. Epidemiology of prostate cancer in Europe. Centre for Parliamentary Studies, 2015 (https://ec.europa.eu/jrc/en/publication/epidemiology-prostate-cancer-europe).
[3] Jemal A, Bray F, Center MM, et al. Global cancer statistics 2011;61(2): 69-90.
[4] Martins T, Ukoumunne OC, Banks J, et al. Ethnic differences in patients' preferences for prostate cancer investigation: a vignette-based survey in primary care. Br J Gen Pract. 2015 Mar;65(632): e161-70.
[5] Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023 Jan;73(1):17-48. doi: 10.3322/caac.21763. PMID: 36633525.
[6] Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet. 2014 Dec 6;384(9959):2027-35. doi: 10.1016/S0140-6736(14)60525-0. Epub 2014 Aug 6. PMID: 25108889; PMCID: PMC4427906.
[7] Vickers A J, Ulmert D, Sjoberg D D, et al. Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40-55 and long term risk of metastasis: case-control study *BMJ* 2013; 346 :f2023 doi:10.1136/bmj.f2023
[8] Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Parker, C. et al. Annals of Oncology, 2020, Volume 31, Issue 9, 1119 - 1134
[9] Ian M. Thompson, Donna Pauler Ankerst, Chen Chi, et al. Assessing Prostate Cancer Risk: Results from the Prostate Cancer Prevention Trial, JNCI: Journal of the National Cancer Institute, Volume 98, Issue 8, 19 April 2006, Pages 529–534, https://doi.org/10.1093/jnci/djj131
[10] Culp, M.B., et al. Recent Global Patterns in Prostate Cancer Incidence and Mortality Rates. Eur Urol, 2020. 77: 38. https://www.ncbi.nlm.nih.gov/pubmed/31493960
[11] W.H.O. Data visualization tools for exploring the global cancer burden in 2020. 2020. 2021. https://gco.iarc.fr/today/home
[12] EAU Guidelines Prostate Cancer, updated 2025, EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/
[13] European Commission. Prostate cancer burden in EU-27. 2021. https://ecis.jrc.ec.europa.eu

seen in all cancer types, the role of androgens connects all the subtypes from localised to advanced prostate cancer. Thus, 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).[14]

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, abnormal multi-parametric magnetic resonance imaging (MRI), atypical small acinar proliferation or multifocal high-grade prostatic intraepithelial neoplasia. The most important prognostic factors are the stage, differentiation, and PSA level at diagnosis.[8]

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.[15] Localised disease should be classified as low-risk (T1-T2a and Gleason score (GS) ≤6 and PSA ≤10), intermediate-risk (T2b and/or GS 7 and/or PSA 10-20) or high-risk (≥T2c or GS 8-10 or PSA >20) as a guide to prognosis and therapy.

Clinical T stage should be evaluated by digital rectal examination. 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 free/total 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.[8]

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 optimal 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.[8,12] 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.[16,17]

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.[18]

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

[14] Grönberg H. Prostate cancer epidemiology. Lancet. 2003 Mar 8;361(9360):859-64. doi: 10.1016/S0140-6736(03)12713-4. PMID: 12642065.
[15] Rao et al. Validation of the WHO 2016 new Gleason score of prostatic carcinoma. Urol Ann 2018;10:324-9.
[16] 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.
[17] 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.

localised prostate cancer.[12,8] Leuprorelin ADT has been shown to improve quality of life and prolong life in prostate carcinoma patients.[18,19]

Clinical pharmacological properties and efficacy and safety of leuprorelin in ADT in neoadjuvant treatment or for treatment of advanced prostate cancer have been well characterised,[18,19] and leuprorelin clinical practice experience comprises about three decades, with the first leuprorelin 1mg products required to be injected at a daily basis, followed by more convenient leuprorelin depot forms during the last 20 years.

2.2. Aspects of development

No scientific advice from the CHMP was sought by the MAH for this procedure.

In terms of clinical pharmacology, efficacy and safety, the Applicant relies on data of the reference product Eligard 22.5 mg, which was approved in the EU in Germany first, in 2003 (Eligard 22.5 mg, DE/H/0508/002). The iMAA for Camcevi (EMEA/H/C/005034) was submitted under Article 10(3) of Directive 2001/83/EC. For the marketing authorisation approval of this line extension application, it is mandatory to show the bridging between Camcevi 21 mg and the EU-sourced reference product Eligard 22.5 mg. According to the EMA guideline: "Test products in an application for a generic or hybrid product or an extension of a generic/hybrid product are normally compared with the corresponding dosage form of a reference medicinal product, if available on the market".[20]

The Applicant conducted a pivotal phase 3 clinical trial (Study FP01C-17-001). The study also examined serum pharmacokinetics of Camcevi 21 mg. Additionally, to bridge the non-clinical and clinical safety data of the first approved leuprorelin (Lupron 1 mg), an in silico study comparing the steady-state PK parameters of Camcevi 21 mg and Lupron 1 mg for daily injection was conducted (FP01N-24-001). This bridging exercise was further extended by cross-study PK comparisons of Camcevi 21 mg, Camcevi 42 mg, and other leuprorelin depot forms (Lupron 22.5 mg, Lucrin, Eligard) to demonstrate comparable leuprorelin exposure within the established therapeutic range of 0.2 to 2.0 ng/mL (Study FSEE-PMX-FP001-1605).

Currently, one clinical study (FP01C-17-001) and two modelling reports (study FP01N-24-001 and study FSEE-PMX-FP001-1605) are included in this line extension.

2.3. Description of the product

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. This GnRH agonist leuprorelin 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 oestradiol 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 $\leq$ 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

[18] 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.
[19] Sethi R, Sanfilippo, N. Six-month depot formulation of leuprorelin acetate in the treatment of prostate cancer. Clin Interv Aging 2009;4:259-267.
[20] European Medicines Agency. Guideline on the investigation of bioequivalence. 2010, page 7. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf

leuprorelin levels are maintained within an established therapeutic range (0.2 to 2.0 ng/mL) to produce affective serum testosterone suppression.

This is an extension of MA of leuprorelin mesilate injectable suspension Camcevi 21 mg, supplied as ready-to-use drug product in contrast to the available 3-monthly dosed products requiring pre-mixing prior SC injection. The Camcevi 21 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. Camcevi 21 mg is foreseen for a single SC injection every three months, in line with other approved leuprorelin-containing depot formulations of comparable leuprorelin strength (e.g., the reference product Eligard 22.5 mg).

The Camcevi 21 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 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, Camcevi 21 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.

3. Quality aspects

Introduction

This line extension seeks to introduce a new lower, 21 mg strength, of Camcevi to the already authorised 42 mg prolonged-release suspension for injection.

The finished product is presented as prolonged-release suspension for injection containing leuprorelin mesilate equivalent to 21 mg leuprorelin as active substance.

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

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

3.1. Active substance

The active substance in Camcevi 21 mg prolonged-release suspension for injection is leuprorelin mesilate. An Active Substance Master File was provided, which is the same version as approved for Camcevi 42 mg strength. The information provided by the applicant for the active substance is also in line with Camcevi 42 mg strength.

3.2. Finished medicinal product

3.2.1. Description of the product and pharmaceutical development

Camcevi 21 mg is a prolonged-release suspension for injection that is intended for subcutaneous administration. It is an off-white to pale yellow viscous and opalescent suspension.

The composition of Camcevi 21 mg has been provided.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. or in-house standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The aim of the pharmaceutical development was to develop a stable, prolonged-release formulation of leuprorelin to be filled into a single, ready-to-use syringe. The development of Camcevi 21 mg took into account all the knowledge acquired during the development of Camcevi 42 mg, the previously approved prolonged-release suspension for injection that delivers leuprorelin over a six-month period.

The Applicant has applied Quality by design (QbD) principles in the development of the finished product and its manufacturing process. However, no design spaces were claimed for the manufacturing process of the finished product.

Quality target product profile (QTPP) and critical quality attributes (CQAs) of the finished product have been presented. The QTPP was defined as a ready-to-use medicinal product in pre-filled syringe, with sustained release for three months, having a pharmacokinetics/pharmacodynamics profile similar to Eligard.

Formulation development of Camcevi 21 mg focused on the selection of the salt form of leuprorelin and polymer composition. Sufficient stability and in vitro dissolution properties of the finished product were

achieved. Both products contain the same amount of leuprorelin base, 21 mg. Real-time in vitro dissolution studies show that leuprorelin is released from Camcevi 21 mg and EU-Eligard 22.5 mg over a three-month period.

Overall, functions of each of the chosen compound and their critical material attributes as well as compatibility of the excipients with the active substance have been adequately discussed. The impact of the critical material attributes on Camcevi CQAs has been evaluated using prior knowledge or by conducting specific studies. All critical material attributes that could affect the finished product CQAs are controlled in the raw material specifications.

The development of the manufacturing process has been described in sufficient detail.

The quality of the clinical batch has been demonstrated to be comparable to that of scale-up batches manufactured using the proposed commercial process.

The choice of terminal sterilisation by gamma irradiation has been adequately justified. Terminal sterilisation by gamma irradiation causes degradation of leuprorelin. No overage of the active substance is used to compensate this degradation. The initially proposed lower assay limit for the release specification has been tightened during the procedure to respond to a MO, which was adequately addressed. In addition the applicant is recommended to consider adding an overage of the active substance to compensate the degradation (REC).

The primary packaging is pre-filled syringe (cyclic olefin copolymer, closed with bromobutyl elastomeric grey tip cap, plunger and finger grip). The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

3.2.2. Manufacture of the product and process controls

The finished product is manufactured at one site. For all sites involved in the manufacture, control and batch release of the finished product sufficient evidence of GMP compliance has been provided.

The manufacturing process is considered to be a non-standard manufacturing process and has been adequately described. It consists of 4 main steps: compounding under vacuum, filtering, filling, and terminal sterilisation. After sterilisation, the syringes are visually inspected, and container closure integrity testing, and labelling are performed. Secondary packaging is then performed.

The initially proposed manufacturing site was unable to complete the required process validation within the timeframe of the line extension procedure, and a major objection was raised, as the manufacturing process is considered non-standard. To resolve the major objection, the manufacturing process was transferred from the initially proposed site to another site, which is a site already approved for the manufacture of Camcevi 42 mg. Process validation has been successfully completed using three consecutive production-scale batches. Terminal sterilisation process by gamma irradiation has been suitably validated in line with relevant ISO standards to ensure that a sterility assurance level (SAL) of 1×10^{-6} is achieved.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Comparative batch analysis has been provided for batches manufactured at the initially proposed site including the batch used in the clinical trial, and the three validation batches produced at the current site. The results confirm that the quality of the finished product is equivalent across the two sites.

3.2.3. 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 (Eur. Ph), water content (Eur. Ph), content uniformity (Eur. Ph & in-house), assay (in-house), degradation products (in-house), residual alkyl methanesulfonates (GC-MS), accelerated release in vitro (in house), average molecular weight by weight of polymer by GPC-RI (in-house), average molecular weight by number of polymer by GPC-RI (in-house), polydispersity by GPC-RI (in-house), particulate matter (Eur. Ph.), breakloose force (in-house), glide force (in-house), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.).

The finished product specifications include appropriate tests for the pharmaceutical form according to ICH Q6A, and the Ph. Eur. monograph for parenteral preparations. In addition, functionality of the syringes is controlled with suitable tests at release and during shelf-life.

The acceptance criteria of the tests have been established based on the Ph. Eur., ICH guidance, information on the active substance, pharmaceutical development, and stability studies. The proposed limits have been satisfactorily justified.

Initially, the applicant proposed a wider assay limit. The applicant did not provide sufficient justification for the proposed limit, a major objection was raised. This issue was resolved when the assay limit was revised.

In addition, the initially proposed specification range for the average molecular weight by weight (Mw) was considered too wide. A major objection was raised requesting the limit to be tightened based on the batch used in the clinical trial. In addition, the limits for the average molecular weight by number (Mn) and polydispersity were required to be revised, as appropriate. The applicant agreed to adjust these limits accordingly, thereby resolving the major objection.

The specified impurities are identical to those found in Camcevi 42 mg. These impurities are controlled in Camcevi 21 mg using the same limits at release and during shelf-life as approved for Camcevi 42 mg.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment 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 (as requested) 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 are the same as those used for Camcevi 42 mg with minor modifications. They have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards has been presented.

Batch analysis results are provided for five commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

3.2.4. Stability of the product

Stability data from three pilot scale batches of finished product stored for up to 36 months under long term conditions (2–8 °C) and for up to 6 months under accelerated conditions (25 °C / 60 % RH) were provided. In addition, data from commercial scale batches stored for up to 30 months at long-term conditions and up to 6 months at accelerated conditions were provided.

The stability batches are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

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

Under long-term storage conditions, the data demonstrate a decreasing trend for assay and molecular weight, and an increasing trend for water content and impurities. Nevertheless, all parameters remained well within specification through 30 months for all batches.

The studies under accelerated conditions indicate that Camcevi 21 mg is heat-sensitive, which are consistent with the observations for Camcevi 42 mg strength. Therefore, Camcevi 21 mg should be stored at 2–8 °C as the already authorised higher strength.

Stability studies under long-term and accelerated conditions for the three process validation batches were initiated. The manufacturing process implemented at the commercial site is not expected to impact the stability of the finished product in comparison with batches manufactured at the initially proposed site. The stability studies will continue throughout the proposed shelf-life in accordance with the stability protocol outlined in section P.8.1. In accordance with EU GMP guidelines[21], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

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

The performed freeze thaw studies confirm that the product is not sensitive to short temperature excursions, and there is no need to include statement "Do not freeze" in the product information.

Based on available stability data, the proposed shelf-life of 30 months with storage conditions "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) are acceptable.

3.2.5. Adventitious agents

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

3.3. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the 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.

[21] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

During the procedure three Major Objections have been raised, pertaining to: 1) Lack of process validation data; 2) Tightening of the assay limit in the release specification; 3) Tightening of average molecular weight by weight, average molecular weight by number and polydispersity specification limits.

In response, the applicant has provided adequate data of three consecutive production-scale batches produced and tightened the assay limits, the average molecular weight by weight limit and the average molecular weight by number and polydispersity limits as requested.

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 finished product.

At the time of the CHMP opinion, there was one minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertain to the fact that the applicant does not use any overage of the active substance to compensate the degradation due to terminal sterilisation by gamma irradiation. The applicant is recommended to consider adding an overage of the active substance to compensate the degradation. This point is put forward and agreed as recommendation for future quality development.

3.4. 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.

3.5. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- to consider adding an overage of the active substance in the finished product to compensate the degradation that occurs during terminal sterilisation. If this approach is chosen, it can be managed post-authorisation through a suitable variation application in line with the variation guideline.

4. Non-clinical aspects

Introduction

Based on the wide use and the well-established clinical efficacy and safety profile of leuprorelin prolonged release formulations in the proposed indication, an abbreviated nonclinical program using Eligard 22.5 mg as a reference medicinal product was conducted to support clinical development of Camcevi 21 mg. This abbreviated program consisted of two single dose studies in male rats (***Study FP01N-14-001 and*** **Study FP01N-17-007***)* evaluating the pharmacokinetic and pharmacodynamic (PK/PD) profile (serum leuprorelin and testosterone concentrations) of various formulations during development following single dose subcutaneous administration with follow up periods of 3 months and one single-dose Good Laboratory Practice (GLP) toxicity study in male rats up to 3 months **(Study FP01N-16-001).** The nonclinical safety of Camcevi 21 mg is based on the combination of: reliance on the Agency's findings of safety for the reference medicinal product, Eligard 22.5 mg; pharmacodynamic, pharmacokinetic, and toxicity studies conducted with Camcevi 21 mg. Supportive data are included from the Camcevi 42 mg (EMEA/H/C/005034) development and additional supportive information provided by the published literature.

Analytical methods

A validated LC-MS/MS method was used to determine leuprorelin and testosterone in rat serum. Linearity, precision, accuracy, selectivity, dilution, extraction recovery, matrix effect, gender effect, injection carryover, and stability were evaluated. The methods were used to support the PK/PD study FP01N-14-001, the non-GLP PK/PD study FP01N-17-007, and the GLP toxicity study FP01N-16-001 with Camcevi 21 mg drug product.

A HPLC-UV method for the determination of leuprolide in dose formulation was originally validated () and followed by partial validation (). Linearity, sensitivity, accuracy, precision, solvent blank evaluation, injection carryover, and stability were evaluated. The methods were used to support the GLP toxicity study FP01N-16-001 with the Camcevi 21 mg drug product.

All bioanalytical methods were validated and study samples were analysed. The methods are appropriate for the non-clinical studies. The performance of the bioanalytical methods was satisfactory during the sample analysis

4.1. Pharmacology

4.1.1. Pharmacodynamics

4.1.1.1. Primary pharmacodynamics

The expected pharmacological effect of a long-acting (3-month) leuprorelin mesilate injectable product Camcevi 21 mg (referred to as LMIS 25 mg for leuprorelin mesylate salt), an initial rise in serum testosterone level followed by a continuous suppression of the serum testosterone level below normal levels, was demonstrated by two single dose subcutaneous pharmacokinetic and pharmacodynamic (PK/PD) studies in male rats. These studies included the PK/PD profiling (serum leuprorelin and testosterone

concentrations) of various formulations during development following single dose subcutaneous administration with follow up periods of 3 months.

The first single-dose PK/PD study (**Study FP01N-14-001**) characterized the pharmacology of 7 different leuprorelin mesilate depot (sustained-release) formulations (LMIS) compared to a single SC administration of vehicle in Sprague-Dawley (SD) male rats.

The dosing regimen is presented in *Table 4*.

Table 1: Dosing regimen: single-dose subcutaneous administration.

Group No. [a]	***Name TA/RA***	***Label Strength***	***Dose Weight (mg)***	***LA concentration (Free base, w/w)***	***Dose (mg, free base)***
1	*Form-1, TA*	*LMIS 25mg*	*150*	*7%*	*10.5*
2	*Form-2, TA*	*LMIS 12.5mg*	*150*	*3.5%*	*5.25*
3	*Form-3, TA*	*LMIS 25mg*	*150*	*7%*	*10.5*
4	*Form-4, TA*	*LMIS 25mg*	*150*	*7%*	*10.5*
5	*Form-5, TA*	*LMIS 25mg*	*150*	*7%*	*10.5*
6	*Form-6, TA*	*LMIS 12.5mg*	*150*	*3.6%*	*5.4*
7	*Form-7, RA*	*LMIS 50mg*	*150*	*11.7%*	*17.6*
8	*Saline*	*Control*	*150*	*0*	*0*

[a] *Number of male animals in all groups: n = 3*

LA = leuprorelin; LMIS = Leuprorelin Mesilate injectable suspension, TA/RA = test article/reference article

All groups treated with LMIS formulations sustained testosterone suppression below the human castration level through 91 days. In LMIS 25 mg treated groups, the mean serum testosterone concentrations were decreased to castrate levels (below 0.500 ng/mL) at 7 days post-dose in Groups 1 and 4 and at 28 days post-dose in Group 5. In LMIS 12.5 mg treated groups, the mean serum testosterone concentrations were decreased to castrate levels at 7 days post-dose in Group 6 and at 21 days post-dose in Group 2. Following subcutaneous administration of LMIS 50 mg in Group 7, the mean serum testosterone concentrations were decreased to castrate levels at 21 days post-dose. No difference in PD based on polymer composition was observed (PLA or PLGA and NMP).

The second PK/PD study (**Study FP01N-17-007**) compared the pharmacology of different LMIS 25 mg (Camcevi 21 mg) formulations, containing different batches of PLGA, against vehicle control over a period of 3 months following a single SC injection in Sprague-Dawley male rats. This study was conducted as a part of the quality-by-design (QbD) study to assess the quality attributes (inherent viscosity of the polymer) of four different LMIS 25 mg test article batches, and their potential impacts to product in in vivo performance compared to a single SC administration of vehicle in Sprague-Dawley rats. In addition, *in vitro*/*in vivo* correlations (IVIVC) analyses of leuprorelin were assessed and reported. A total of 30 male rats were assigned into 5 groups of 6 animals each. The five groups included one vehicle (LMIS 25 mg control CC0540) treated-group (N=6 rats, Group 1) and four test article-treated groups (N=6 rats/group, Groups 2 to 5): LMIS 25 mg Prelim-design of experiment (DoE) batch# 1 (Group 2), LMIS 25 mg Prelim-DoE batch# 2 (Group 3), LMIS 25 mg Prelim-DoE batch# 3 (Group 4) or LMIS 25 mg Prelim-DoE batch# 4

(Group 5) via a single SC administration (Table 5 and Table 6). Following SC administration of LMIS 25 mg, serum testosterone concentration gradually decreased from Day 7 up to Day 28. Serum testosterone levels remained low (castrate levels of 0.5 ng/mL) until the end of study (3 months) for the majority of LMIS formulations except for Formulation 3, for which the magnitude of reduction was less pronounced, despite displaying the highest leuprorelin PK exposure (AUC_{last}) observed over the 3-months period. The minimum testosterone level observed (R_{min}) was approximately 2 to 5-fold higher for LMIS formulation 3 than the other formulations. The serum testosterone exposure (AUEC $Below t_{hreshold}$) and the time spent below the castrate level (T $Below_{threshold}$) were much lower with formulation #3 by approximately 32- and 6-fold, respectively (in comparison to formulations 1, 2 and 4) (Table 7). Although serum testosterone concentration was highly variable among LMIS batches, all formulations were able to effectively suppress testosterone in rats to the same extent over at least 92 days. This is in line with primary pharmacodynamic studies formerly conducted with Camcevi 42 mg.

Table 2: Study design/treatment groups.

Group No.	**Batch#**	**Dose Level**[a] (mg/animal)	**Injection Weight**[b] (mg/animal)	**Number of Males**
1	CC0540 (placebo)	0	150	6
2	Prelim-DoE batch#IV1	~ 10.1	150	6
3	Prelim-DoE batch#IV2	~ 10.1	150	6
4	Prelim-DoE batch#IV3	~ 10.1	150	6
5	Prelim-DoE batch#IV4	~ 10.1	150	6

[a] Based on leuprorelin salt (uncorrected with purity) content
[b] Based on the formulation weight or volume. Target range of injection weight: ±10%.
DoE = design of experiment; Prelim = preliminary

Pharmacodynamic data was additionally collected from one single dose Good Laboratory Practice (GLP) toxicity study (**Study FP01N-16-001**) conducted with Camcevi 21 mg in comparison to two marketed leuprorelin acetate products (Eligard 22.5 mg (EU and US) and Lupron Depot 22.5 mg (US)). All single SC dose levels (3.4, 10.1, and 16.9 mg leuprorelin mesylate/rat) in male SD rats (10-week old at dosing) were able to reduce serum testosterone to below normal castrate levels ($\leqslant$ 0.5 ng/mL) until termination in all leuprorelin-treated animals, similar to a 15 mg/rat and 3.0 mg/rat single SC or IM dose of the two reference drugs, Eligard 22.5 mg and Lupron Depot 22.5.mg. Reduced serum testosterone level to the castrate level was noted starting on Days 15 (Eligard 22.5 mg at 15.0 mg/animal), 29 (LMIS 25 mg at 3.4, 10.1 and 16.9 mg/animal), and 57 (Lupron Depot 22.5 mg at 3.0 mg/animal). A pharmacodynamic effect of suppressed testosterone was anatomically ensured by atrophy of male sex organs.

Data in the published literature explored the pharmacodynamics of immediate- and sustained-release leuprorelin acetate administered by SC or IM route in mice, rats, and dogs and found similar results regarding repression of serum testosterone and size of male sex organs. Furthermore, leuprorelin treatment could inhibit the growth of prostate and liver tumors in rats and mice. The target organ profile in the 3-month study performed by the Applicant is consistent with findings in the previous Camcevi 42 mg studies, and also in the leuprorelin acetate 2-year carcinogenicity studies and the primary pharmacodynamic effects of GnRH agonism.

4.1.1.2. Secondary pharmacodynamics

No secondary pharmacodynamic studies have been conducted with leuprorelin. Leuprorelin is a well-known compound. Given its decades of use in the proposed indication, sufficient clinical information is available which supersede animal data.

4.1.1.3. Safety pharmacology

No studies were conducted. Leuprorelin is a well-known compound. Given its decades of use in the proposed indication, sufficient clinical information is available which supersede animal data.

In the completed single dose toxicity study in rats, no differences were observed in clinical signs between Camcevi 21 mg and the reference medicinal product Eligard 22.5 mg.

4.1.1.4. Pharmacodynamic drug interactions

No studies were conducted. Leuprorelin is a well-known compound. Given its decades of use in the proposed indication, sufficient clinical information is available which supersede animal data.

4.1.2. Pharmacokinetics

4.1.2.1. Absorption

The free base equivalent is the same between the proposed Camcevi 21 mg product and the currently approved 21 mg leuprorelin acetate product Eligard 22.5 mg powder and solvent for solution for injection (Eligard 22.5 mg), which is used as a reference product in this hybrid application. During the development of Camcevi 21 mg, two PK/PD combination studies following a single dose SC administration with follow up period 3 months were conducted in male SD rats to characterize the PK profile of leuprorelin, and the correlating testosterone levels.

In the first PK study (**Study FP01N-14-001**), absorption of different leuprorelin mesilate depot formulations of Camcevi 21 mg and 12.5 mg were compared against Camcevi® 42 mg (reference control) over a period of 3 months following a single SC injection. The median time to peak drug concentration values (T_{max}) of leuprorelin were reached at the first sample time, 0.17 days, following dosing in all leuprorelin -treated groups except for two formulations, which were reached at 28 days post-dose. There was a significant variation in dose normalized C_{max} and $AUC_{0\text{-}91day}$ values between tested formulations and in comparison to the reference control.

In the second PK study **(Study FP01N-17-007**), as a part of the quality-by-design (QbD) study to assess the quality attributes of LMIS 25 mg, and their potential impacts to product in in vivo performance (impact on leuprorelin and testosterone exposure) of PK/PD of four LMIS 25 mg batches was determined. Additionally, the feasibility of an *in vitro*/*in vivo* correlation (IVIVC) in rats was explored. Following a single SC administration of LMIS 25 mg in rats, an initial burst phase was observed during the first 24 hours, which was followed by a maintenance phase. Leuprorelin displayed distinct flip flop kinetics with multiple concentration peaks observed during the sustained release period. LMIS 25 mg formulations had an impact on leuprorelin peak concentrations (C_{max}), but no significant impact on testosterone concentrations except for batch #3.

Additional PK/PD data were collected from GLP-compliant 3-month single SC dose toxicity study in rats. The study utilized single dose levels of LMIS 25 mg (3.4, 10.1, and 16.9 mg leuprorelin mesilate/rat) followed by 3 months post-dose duration. Two marketed leuprorelin acetate reference products, Eligard 22.5 mg and Lupron Depot 22.5 mg, were included. The mean T_{max} values of leuprorelin were reached at 0.17 days. Between Eligard 22.5 mg-treated group at 15.0 mg/animal and LMIS 25 mg-treated group at 16.9 mg/animal, the $AUC_{0\text{-}91day}$ was similar but the C_{max} was approximately 2-fold higher in the Eligard 22.5 mg-treated group than that in LMIS 25 mg-treated group at 16.9 mg/animal. LMIS 25 mg-treated group at 3.4 mg/animal had approximately 3- and 11-fold higher C_{max} and $AUC_{0\text{-}91day}$, respectively, compared to the Lupron Depot 22.5 mg-treated group at 3.0 mg/animal.

The LC-MS/MS method was developed and validated for the simultaneous determination of leuprorelin and testosterone in rat serum. See Section: *Analytical methods*.

4.1.2.2. Distribution

No nonclinical distribution studies have been conducted by the Applicant to demonstrate the distribution of Camcevi 21 mg or leuprorelin mesylate. Distribution is reported for Eligard 22.5 mg (Eligard® SmPC) as "*In vitro binding to human plasma proteins ranged from 43% to 49%*."

The study of Arulsudar et al. (2024) was presented and is summarised as follows: Distribution of leuprorelin acetate was measured as free drug and as liposome-encapsulated in conventional (LL) or sterically stabilized in PEG of molecular weight 5000 (SLL5000) or 2000 (SLL2000) in ehrlich ascites tumor-bearing Balb/C mice (aged 2-3 months). The $T_{1/2}$ of liposome-encapsulated leuprorelin was greater than the drug in its free state. The percentage injected dose/g of tissue in different organs at different time intervals for free drug is shown in Table 8 and for liposome-encapsulated drug in Table 9: Biodistribution of LL, SLL5000, and SLL2000 in tumor-bearing mice (Arusudar et al, 2024). Sterically stabilized liposomes demonstrated an improved distribution pattern compared with conventional liposomes.

4.1.2.3. Metabolism

No nonclinical metabolism studies have been conducted by the Applicant to demonstrate the metabolism of Camcevi 21 mg or leuprorelin mesylate. Instead, two reports from published scientific literature were cited.

In the report of Sofianos et al. (2008), the *in vitro* metabolism of leuprorelin was evaluated using mouse kidney membrane preparations at 0.5, 1, and 2 hours. Two metabolites were detected, the major one was the pentapeptide M– I (Tyr5-D-Leu6-Leu7-Arg8-Pro9-NHC2H5) and the minor metabolite, the tripeptide M–III (pGlu1- His2-Trp3-OH).

In the publication of Okada et al. (1991), serum levels of leuprolide acetate (LA) and its metabolite, M-I, were measured in rats after SC injection of 3 mg/kg LA microspheres (PGLA). The serum level of M-I was 21% of the intact drug 3 h after injection but decreased to 3.4% to 6.7% 1-3 weeks after injection and was not detectable after 4 weeks.

4.1.2.4. Excretion

No nonclinical excretion studies have been conducted by the Applicant to demonstrate the excretion of Camcevi 21 mg or leuprorelin mesilate. The excretion of leuprorelin acetate as demonstrated in the published literature is summarized below.

In the publication of Okada et al. (1991). Microspheres were also chronically injected 3 mg/kg SC (1 injection every 4 weeks, a total of 3 times) into male (10 weeks of age) and female (11 weeks of age) rats. Urinary excretion was calculated as a percentage of the theoretical 1-day dose, assuming that leuprorelin is constantly released from the microspheres. The percentage excreted at Day 0 after each injection was 3.5 - 4 times higher than that calculated by the theoretical 1-day dose. The excretions at Days 2 and 7 were both about 13.5% for both male and female rats. A second peak arose at Day 14 of 23.5 ± 1.2% for males and 21.6 ± 0.8% for females. The excretion decreased to about 5% at Day 21 and was not detectable at Day 56. The authors concluded that the excretion of the drug is not changed and there is no accumulation of the drug in the body after repeated injection of the microspheres.

4.1.2.5. Pharmacokinetic drug interactions

No pharmacokinetic-based drug-drug interaction studies have been conducted with leuprorelin acetate. However, because leuprorelin acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P450 enzymes as noted in specific studies, and the drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur (AbbVie Inc, 2018).

4.1.2.6. Other pharmacokinetic studies

No other pharmacokinetic studies were conducted with Camcevi 21 mg.

4.2. Toxicology

The Applicant conducted one single-dose Good Laboratory Practice (GLP) toxicity study (Study FP01N-16-001) with Camcevi 21 mg including two marketed leuprorelin acetate reference products, Eligard® 22.5 mg (DE/H/0508/002) and Lupron Depot® 22.5 mg. Eligard 22.5 mg is a leuprorelin acetate injectable suspension with a 3-months extended-release profile. It contains poly (DL-lactide-co-glycolide) (PLGA) and N-methyl-2-pyrrolidone (NMP) in a 45:55 ratio (Eligard® SmPC, 2022).

4.2.1. Single-dose toxicity

Study FP01N-16-001: LMIS 25 mg: A 3-Month Single Subcutaneous Dose Toxicity Study in Rats (GLP)

The purpose of this study was to determine the toxicokinetics (TK), pharmacodynamics (PD) and potential toxicity of Camcevi 21 mg following a single SC injection in male Sprague-Dawley rats over a period of 3 months. Each 10-week-old rat received a single administration of treatment as outlined in Table 10.

Table 3: FP01N-16-001 study design.

Group	Treatment Type	Leuprorelin Dose Level (mg/animal)		Injection Route[a]	Injection Weight/Volume	Number of Males
		Salted Base	Free Base			
1	Vehicle Control (LMIS 25 mg-placebo)	0	0	SC	250 mg/animal	5[b]+ 5[c]
2	Sham Control (saline)	0	0	SC	250 mg/animal	5[b]+ 5[c]
3	Reference Article 1 (Eligard 22.5 mg)	15.0	14.0	SC	250 mg/animal	5[b]+ 5[c]
4	Reference Article 2 (Lupron Depot 22.5 mg)	3.0	2.8	IM	0.2 mL/site /animal	5[b]+ 5[c]
5	Test Article (LMIS 25 mg)	3.4	3.0	SC	50 mg/animal	5[b]+ 5[c]
6	Test Article (LMIS 25 mg)	10.1	8.8	SC	150 mg/animal	5[b]+ 5[c]
7	Test Article (LMIS 25 mg)	16.9	14.7	SC	250 mg/animal	5[b]+ 5[c]

[a] subcutaneous (SC) injection, intramuscular (IM) injection.

[b, c] The treatment groups consisted of 2 cohorts (subgroups 1 and 2): the dosing of each subgroup was staggered over 2 days.

Vehicle control article (LMIS 25 mg placebo), sham control article (saline), reference article 1 (Eligard 22.5 mg:), or test article (LMIS 25 mg) was administered SC to the rats on Day 1. Reference article 2 (Lupron Depot 22.5 mg) was administered intramuscularly (IM) to the rats on Day 1. All animals were terminated on Day 92 for necropsy.

The following parameters were evaluated in this study: mortality/moribundity, clinical signs, body weight, food consumption, clinical pathology (hematology, coagulation, serum chemistry, and urinalysis), TK, PD based on serum testosterone levels, and pathology (necropsy, gross examination, organ weight, and histopathology of all main toxicity study tissues for Groups 1, 3, 5, 6, and 7). Microscopic examination was performed on target tissues of leuprorelin (pituitary, testis, epididymis and prostate/seminal vesicle) determined by the previous 3-month and 6-month studies of LMIS 50 mg (FP01N-13-001 (GLP).

All animals survived until terminal necropsy on Day 92 without moribundity. Hematology data and serum chemistry did not reveal leuprorelin-related changes. Leuprorelin-related change was limited to the decreased testis size observed in test article treated groups as well as Eligard 22.5 mg- and Lupron Depot 22.5 mg-treated groups. SC dose-related subcutaneous mass was evident in all groups. Leuprorelin-related changes were slightly decreased body weights (5-11% decreases) and body weight gain (18-32 % decreases) noted in all leuprorelin-treated groups. The body weight decrease was considered to be related to reduced food intake. shortened prothrombin time (13-19% shortening) noted in all leuprorelin-treated groups without changes in activated partial thromboplastin time. Leuprorelin-related decrease in incidence and number of sperms was observed in urine sediments of all leuprorelin-treated groups compared to the vehicle control (LMIS 25 mg placebo) and sham control (saline) groups.

Toxicokinetics

TK parameters are shown in Table 11

Table 4: Systemic exposure to leuprorelin.

Group/Treatment Type	**Dose Level[a] (mg/animal)**	**C_{max} (ng/mL)**	**$AUC_{0\text{-}91\ day}$ (day·ng/mL)**
Group 3/Eligard 22.5 mg	15.0	428	1,600
Group 4/Lupron Depot 22.5 mg	3.0	39.4	52.6
Group 5/LMIS 25 mg	3.4	105	583
Group 6/LMIS 25 mg	10.1	217	1,340
Group 7/LMIS 25 mg	16.9	191	1,700

[a] As leuprorelin acetate for Eligard 22.5 mg and Lupron Depot 22.5 mg, and leuprorelin mesilate for LMIS 25 mg.
$AUC_{0\text{-}91day}$ = area under the curve from time 0 to 91 days; C_{max} = maximum plasma concentration

The mean time to reach maximum serum concentration (T_{max}) was 0.17 days for all dose groups. In LMIS 25 mg-treated groups, the mean leuprorelin concentrations increased again starting at 14 (10.1 mg/animal) and 28 days (3.4 and 16.9 mg/animal) postdose with the second peaks at 42 to 70 days postdose. In Eligard 22.5 mg treated group (15.0 mg/animal), mean leuprorelin concentration decreased gradually from 14 days postdose. In Lupron Depot 22.5 mg-treated group (3.0 mg/animal), low concentrations (0.1-0.3 ng/mL) were maintained from 14 to 91 days postdose.

Pharmacodynamics

Table 5: Serum testosterone concentration summary.

Timepoint (day postdose)	**Serum Testosterone (ng/mL)**						
	GP1 vehicle	**GP2 Sham control**	**GP3 Eligard**	**GP4 Lupron Depot**	**GP5 LMIS 25mg**	**GP6 LMIS 25 mg**	**GP7 LMIS 25 mg**
Pre-dose	3.08	3.14	4.39	4.29	4.42	5.33	3.64
0.17	1.59	2.06	16.5	17.6	15.0	17.0	15.5
1	2.66	3.45	8.72	8.19	7.12	7.55	7.51
2	2.87	3.66	3.05	3.06	2.97	3.07	2.81
7	3.28	4.05	0.885	1.16	0.896	0.968	0.897
14	2.81	3.23	0.404	0.769	0.513	0.523	0.507
28	3.83	4.42	0.329	0.637	0.344	0.287	0.318
42	3.12	2.95	0.269	0.550	0.323	0.271	0.304
56	3.11	2.91	0.248	0.437	0.404	0.264	0.303
70	1.52	1.66	0.256	0.387	0.342	0.218	0.311
91	1.11	1.61	0.267	0.495	0.295	0.217	0.306

Group 1 (GP1) = vehicle control, GP2 = sham control, GP3 = Eligard 22.5 mg at 15.0 mg/animal,
GP4 = Lupron Depot 22.5 mg at 3.0 mg/animal, GP5 = LMIS 25 mg at 3.4 mg/animal,
GP6 = LMIS 25 mg at 10.1 mg/animal, GP7 = LMIS 25 mg at 16.9 mg/animal.

Organ Toxicity
The target organs of leuprorelin were the pituitary and male reproductive organs including testis, epididymis, and prostate/seminal vesicle.

- Pituitary: focal hyperplasia in LMIS 25 mg-treated group at 16.9 mg/animal, Eligard 22.5 mg- and Lupron Depot 22.5 mg-treated groups
- Testis: germ cell depletion, tubular atrophy, coagulative necrosis/mineral deposition, and decreased size and weight in all leuprorelin -treated groups (LMIS 25 mg, Eligard 22.5 mg, and Lupron Depot 22.5 mg); discoloration in LMIS 25 mg-treated groups at 3.4 and 10.1 mg/animal and Eligard 22.5 mg-treated group
- Epididymis: reduced epididymal sperm and cellular debris that contributed to reduced urinary sperms; decreased size and weight in all leuprorelin -treated groups (LMIS 25 mg, Eligard 22.5 mg, and Lupron Depot 22.5 mg)
- Prostate/seminal vesicle: decreased size and weight, and atrophy in all leuprorelin treated groups (LMIS 25 mg, Eligard 22.5 mg, and Lupron Depot 22.5 mg).

The pituitary change was considered to be a primary effect of LH-RH agonist. Other target organ changes were effects of decreased testosterone levels. Decreased food consumption and body weight, and shortened prothrombin time were also due to decreased testosterone levels. Decreased heart and kidney weights in all leuprorelin treated groups were considered to be secondary changes to decreased body weight.

Focal hyperplasia of the pituitary was considered to be adverse; therefore, the no-observed-adverse-effect level (NOAEL) of LMIS 25 mg was 10.1 mg/animal at which associated C_{max} and $AUC_{0\text{-}91day}$ were 217 ng/mL and 1,340 day•ng/mL, respectively. In addition, due to absence of severe toxicity severely toxic dose in 10% animal (STD 10) of LMIS 25 mg was above 16.9 mg/animal at which associated C_{max} and $AUC_{0\text{-}91day}$ were 191 ng/mL and 1,700 day•ng/mL, respectively.

Supporting toxicity data were obtained from the Applicant-conducted PK/PD Study FP01N-14-001, in which male SD rats received a single dose of seven different formulations of LMIS (3 animals/group). Clinical findings included erythema and/or oedema around injection sites, hair loss and scratched wounds.

In the published study of Mashayekhi and colleagues (Mashayekhi et al., 2013), *in vitro* and *in vivo* comparison of the leuprorelin release from an *in situ* forming PLGA system were conducted. A PLGA implant was used to control the release profile of leuprorelin acetate drug. The system is an *in-situ* polymeric precipitation system, the formulation consisted of PLGA polymer, leuprorelin acetate (LA) drug, and NMP solvent with no additives. The initial burst release of LA was 14% *in vitro* whereas it was 7% in vivo. *In vitro* and *in vivo* release profiles of LA had similar trends after 72 hours. However, the rate of LA release was slower *in vivo*. All sexual organs and tissues of leuprorelin-exposed female rats were normal suggesting that that the implant did not possess any toxicity effects on the living tissues and organs including the tissues at the injection site and sexual/non-sexual organs.

4.2.2. Repeat-dose toxicity

No nonclinical studies have been conducted by the Applicant to demonstrate the repeat-dose toxicity of Camcevi 21 mg or leuprorelin mesilate. Instead, one relevant literature reference was summarised.

In a study of Cukierski et al. (2001), adult (6 to 8 months of age) male beagle dogs (n = 6) were SC implanted with DUROS leuprorelin implants containing 65 mg leuprorelin and designed to deliver at a nominal rate of 120 µg per day for at least 12 months. After 52 weeks, the implants were removed, and a new DUROS implant was inserted in the contralateral flank for an additional 8 weeks. Additional 4 dogs

received sham operations and 4 were administered IM injections of Lupron Depot 3.75 mg every 28 days as positive controls. All dogs were euthanized on day 421.

All dogs in this study survived to a scheduled termination date. Group mean body weight and mean body weight change data were comparable between treated and control groups. Clinical chemistry and hematology values did not demonstrate any biologically significant treatment-related differences when compared with sham control values. The testes of dogs treated with DUROS leuprorelin implant or Lupron Depot 3.75 mg were notably smaller and atrophic at termination compared with those of sham-operated dogs. There were no gross findings at necropsy other than atrophy of the testes and prostate gland in dogs treated with the DUROS leuprorelin implant or Lupron Depot 3.75 mg. Following chronic exposure to leuprorelin acetate, the weights of the testes and prostate gland in these animals were markedly lower than those of the sham-operated dogs. Mean relative kidney weight as a percent of total body weight was significantly ($p < 0.05$) lowered in Lupron Depot-treated dogs and was reduced, but not significantly, in DUROS leuprorelin -treated dogs, compared with the sham control. The affected testes in leuprorelin-treated dogs showed a significant reduction in weight and were accompanied by obvious germ cell loss. Changes in the epididymides and prostate glands of leuprorelin -treated dogs reflected the effects on the testes. No other treatment-related histomorphologic alterations were observed. ELISA assay was unable to clearly demonstrate the presence of anti- leuprorelin antibodies from dogs that received DUROS leuprorelin implants.

Mean serum leuprorelin concentrations in dogs with DUROS leuprorelin implants were constant over the course of the study, ranging from 0.71 to 9.63 ng/ml with approximately 90% of the values falling between 1.15 and 4.00 ng/ml. Mean leuprorelin concentrations from dogs receiving the Lupron Depot ranged from BLQ to 0.624 ng/ml throughout the study. In 38% of the samples analyzed from this group, leuprorelin concentrations were BLQ.

Serum testosterone concentrations of the individual sham operated dogs showed considerable day-to-day variation in individual dogs. These data are consistent with the published range (43 to 400 ng/dL) for testosterone concentrations in dogs. In all 6 dogs treated with the DUROS leuprorelin implant, testosterone concentrations initially increased from baseline after implantation and then decreased to castrate concentrations (< 50 ng/dL) by day 29 of the study. Serum testosterone levels remained suppressed following removal of the first DUROS leuprorelin implant on day 365 and subsequent insertion of a new DUROS leuprorelin implant. A transient rise in testosterone levels occurred before Lupron Depot reinjection on days 29 and 57 of the study. Testosterone concentrations remained below castrate levels from day 70 to day 420.

4.2.3. Genotoxicity

No genotoxicity studies have been performed with Camcevi 21 mg. A bridge between Camcevi 21 mg and leuprorelin reference medicinal products was established, and reliance on the safety data from the reference medicinal product Eligard is considered appropriate.

4.2.4. Carcinogenicity

No carcinogenicity studies have been performed with Camcevi 21 mg. Carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer.

4.2.5. Developmental and reproductive toxicity

Studies evaluating effects on fertility, early embryonic development and on pre- and postnatal development (including maternal function) with Camcevi 21 mg have not been performed and would not be required for a product developed for the treatment of advanced cancer according to ICHS9.

Regarding the reproductive and developmental toxicity of leuprorelin two relevant literature references were summarised.

In the study of Hori et al. (2028), the histological and cytological changes in the seminiferous tubules of male rats after was observed after receiving the depot formulations of leuprorelin. Atrophic changes were observed as well as markedly reduced wet weight of a testis and mean diameter of seminiferous tubules at 4 weeks after SC administration of adult male Wistar rats (8 weeks of age, body weight: ca. 200 g) with 1.5 mg/kg leuprorelin depot (leuprorelin acetate) for one-month depot suspension (3.75 mg/mL). Long term treatment induced a marked reduction in the height of the epithelium and deformation of apical cytoplasm in Sertoli cells, resulting in premature detachment of spermatids from the epithelium.

In the study of Guarraci et al. (2023), the effects of daily leuprorelin treatment (50 µg/kg, postnatal day (PD) 25–50) on pubertal onset in female (i.e., vaginal opening) and male (i.e., preputial separation) Long-Evans rats was tested. The first estrous cycle immediately after vaginal opening was also measured. Sexual behavior and sexual motivation were tested using the partner-preference paradigm. Female rats were tested during the first behavioral estrus after treatment ended (between PD 51–64). Male rats were tested weekly for four consecutive weeks starting three days after treatment ended (PD 53). Leuprorelin significantly delayed pubertal onset in both female and male rats. In addition, the first estrous cycle during the treatment period was disrupted by leuprorelin, as indicated by a failure to cycle into estrus after vaginal opening until treatment ended. However, leuprorelin affected neither sexual motivation nor fertility when female rats were tested within 14 days of leuprorelin treatment ending. In contrast, the development of copulatory behavior and sexual motivation was significantly delayed by leuprorelin in male rats; however, mature reproductive behavior was observed by the fourth week post-treatment. In conclusion, the present results indicate that male rats may be more sensitive to periadolescent leuprorelin administration, taking longer to overcome the effects of leuprorelin than female rats. The drug's effects were not permanent.

4.2.6. Toxicokinetics and exposure margins

Study FP01N-16-001 **Study FP01C-17-001**[b]

Group/Treatment Type	**Dose Level**[a] **(mg/animal)**	**C_{max} (ng/mL)**	**$AUC_{0\text{-}91\ day}$ (day·ng/mL)**	**C_{max} (ng/mL) 1st dose**	**$AUC_{0\text{-}week12}$, (day·ng/mL) 1st dose**
Group 5/LMIS 25 mg	3.4	105 (2.4x	583 (6.2x)	43.4	93.5
Group 6/LMIS 25 mg	**10.1 (NOAEL)**	217 (5x)	1,340 (14.3x)		
Group 7/LMIS 25 mg	16.9	191 (4.4x)	1,700 (18.2x)		

[a] leuprorelin mesilate for LMIS 25 mg.
[b] Study FP01C-17-001: An Open-Label, Single-Arm Study of the Efficacy, Safety, and Pharmacokinetic Behavior of Leuprolide Mesylate Injectable Suspension (LMIS 25 mg) in Subjects with Prostate Cancer
Exposure margins are shown in parentheses.

TK data of study FP01N-16-001 (LMIS 25 mg: A 3-Month Single Subcutaneous Dose Toxicity Study in Rats (GLP) show large exposure margins compared to the clinical study FP01C-17-001.

4.2.7. Local tolerance

In study FP01N-16-001 no histological changes were observed at injection site.

4.2.8. Other toxicity studies

Not applicable.

4.2.9. Ecotoxicity/environmental risk assessment

Leuprorelin is a synthetic nonapeptide analogue of the naturally occurring gonadotropin releasing hormone (GnRH). Metabolic studies of leuprorelin in animals and humans have shown that *in vivo* leuprorelin is metabolized to smaller inactive peptides. In addition, proteins or peptides, if present in soluble form in the environment, are rapidly degraded. According to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), leuprorelin is exempt from preparation of an Environmental Risk Assessment as the product and excipients do not pose a significant risk to the environment.

4.3. Overall discussion and conclusions on non-clinical aspects

4.3.1. Discussion

Based on the wide use and the well-established clinical efficacy and safety profile of leuprorelin prolonged release formulations in the proposed indication, an abbreviated nonclinical program using Eligard 22.5 mg as a reference medicinal product was conducted to support clinical development of Camcevi 21 mg. This abbreviated program consisted of two single dose studies in male rats evaluating the pharmacokinetic and pharmacodynamic (PK/PD) profile (serum leuprorelin and testosterone concentrations) of various formulations during development following single dose subcutaneous administration with follow up periods of 3 months and one single-dose Good Laboratory Practice (GLP) toxicity study in male rats up to 3 months. The nonclinical safety of Camcevi 21 mg is based on the combination of: reliance on the Agency's findings of safety for the reference medicinal product, Eligard 22.5 mg; PD, PK, and toxicity studies conducted with Camcevi 21 mg. Supportive data are included from the Camcevi 42 mg (EMEA/H/C/005034) development and additional supportive information provided by the published literature.

Developmental and reproductive toxicity were not conducted, which is acceptable according to ICH S9.

As regards genotoxicity and carcinogenicity no own studies have been conducted, instead, the following text from the SmPC of the reference product Eligard is included: *"Carcinogenicity studies were performed in rats and mice over 24 months. In rats, a dose-related increase in pituitary apoplexy was observed after subcutaneous administration at doses of 0.6 to 4 mg/kg/day. No such effect was observed in mice. Leuprorelin was not mutagenic in a set of in vitro and in vivo assays."*

All bioanalytical methods were validated and study samples were analysed. The methods are appropriate for the non-clinical studies. The performance of the bioanalytical methods was satisfactory during the sample analysis.

TK data of a 3-month single subcutaneous dose toxicity study in rats (GLP) show large systemic exposure margins compared to the clinical study FP01C-17-001.

Metabolic studies of leuprorelin in animals and humans have shown that *in vivo* leuprorelin is metabolized to smaller inactive peptides. In addition, proteins or peptides, if present in soluble form in the environment, are rapidly degraded. Therefore, leuprorelin is not expected to pose a risk to the environment.

4.3.2. Conclusions

The presented non-clinical package is considered adequate for extension application to add a new strength of 21 mg for Leuprorelin prolonged-release suspension for injection pre-filled syringe, for subcutaneous (SC) administration.

5. Clinical aspects

Introduction

This is a MA line extension hybrid application to Camcevi 42 mg.

Camcevi 21 mg is a 3-month leuprorelin depot product, provided in a ready-to-use, single sterile, pre-filled syringe, administered via SC injection.

The bridging between Camcevi 21 mg and the EU-sourced reference product Eligard 22.5 mg is presented below.

5.1.1. GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The Applicant claimed that the study FP01C-17-001 was conducted in accordance with the ethical principles of Good Clinical Practice (GCP), according to the International Council for Harmonisation Harmonized Tripartite Guideline. Foresee undertook a GCP audit program to ensure compliance with GCP and to ensure the adequacy of quality control procedures.

One of the sites was closed before the end of study because of GCP violation by site. Five subjects from this site were withdrawn from the study prior to their intended 2nd doses

5.1.2. Tabular overview of clinical trials

One clinical Phase 3, open-label, single-arm study (study FP01C-17-001) was performed to support this application (Table 13).

Table 6: Tabular overview of main clinical studies

Study	Design, control type, duration	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
Phase 3					
An open-label, single-arm study of the efficacy, safety, and pharmacokinetic behavior of leuprolide mesylate injectable suspension (LMIS 25 MG) in subjects with prostate cancer (FP01C-17-001)	Multicenter, SA, OL; 6 months treatment period (24 weeks study drug exposure)	Camcevi 21 mg (leuprorelin free base equivalent) given 12 weeks apart (total of 2 doses); SC	Males with histologically confirmed prostate carcinoma; judged to be candidate for ADT	Study objectives: Primary: To assess the efficacy and safety of Camcevi 21 mg for up to 24 weeks following 2 SC doses given 12 weeks apart in subjects with prostate cancer Secondary: To establish the serum PK profile of leuprolide for Camcevi 21 mg in a subset of subjects with prostate cancer Primary endpoint: To determine the percentage of subjects with a serum testosterone suppressed to castrate levels (≤ 50 ng/dL) on Day 28 ± 1 day (week 4) following administration of Camcevi 21 mg, and the proportion of subjects with serum testosterone suppression (≤ 50 ng/dL) maintained from Day 28 ± 1 day (week 4) through Day 168 ± 5 day (week 24)	Planned: n=133 Enrolled: n=144 Completed: n=129

ADT = androgen deprivation therapy; OL =open label; PK = pharmacokinetic; SA = single arm; SC = subcutaneous

5.2. Clinical pharmacology

5.2.1. Methods

Three bioanalytical methods were used for determination of leuprorelin, testosterone, and luteinising hormone in serum samples from clinical studies. All methods were validated by CRO. This site also performed the analysis of the serum samples.

For the determination of leuprorelin concentrations in human serum an LC-MS/MS (liquid chromatography with tandem mass spectrometry) bioanalytical method was used.

For the determination of testosterone concentrations in human serum an LC-MS/MS bioanalytical method was used.

For the quantitation of luteinising hormone in human serum a commercial ultra-sensitive chemiluminescense ELISA (enzyme-linked immunosorbent assay) method was used.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

The Applicant has conducted a single pivotal clinical Phase 3, uncontrolled, multicenter, open-label, single-arm, 6-month, safety/tolerability, efficacy, and PK/PD study in patients with advanced prostate cancer in

need of androgen ablation therapy to characterize the effects of two subcutaneous doses of Camcevi 21 mg (Study FP01C-17-001). The potential impact of period, race, age, and body weight on serum leuprorelin PK following treatment with Camcevi 21 mg, has been investigated in Report FSEE-NCA-FP001-1341.

In addition, to bridge to the non-clinical and clinical safety information of the first approved leuprorelin (Lupron 1 mg), an *in silico* study of the steady-state PK parameters of Camcevi 21 mg and Lupron 1 mg for daily injection has been performed (FP01N-24-001). The bridging exercise was extended by cross-study leuprorelin PK comparisons of Camcevi 21 mg, Camcevi 42 mg and other leuprorelin depot forms (Lupron, Lucrin, Eligard) to demonstrate comparable leuprorelin exposure within the established therapeutic range (0.2 to 2.0 ng/mL) (Report FSEE-PMX-FP001-1605).

5.2.2.2. Evaluation and qualification of models

Two modelling reports were submitted:

- FP01N-24-001, as part of a bridging exercise to support the reliance of Camcevi 21 mg on clinical and non-clinical safety information of Lupron® Injection 1 mg, the very first approved leuprorelin anywhere.
- FSEE-PMX-FP001-1605, cross-study leuprorelin PK comparisons of Camcevi 21 mg, Camcevi 42 mg, and further leuprorelin depot forms (Lupron, Lucrin, Eligard) to demonstrate comparable leuprorelin exposure within the established therapeutic range (0.2 to 2.0 ng/mL).

The objective of modelling and simulation (M&S) report **FP01N-24-001** was to contrast the steady state levels of leuprorelin following repeated every 3 months (Q3M) subcutaneous (SC) administration of Camcevi 21 mg (aka LMIS 25 mg) to those following repeated once daily (QD) intravenous (IV) administration of leuprorelin (Lupron) 1 mg. Leuprorelin exposure parameters for Camcevi 21 mg SC Q3M were obtained from observed data in the main clinical study FP01C-17-001. Leuprorelin PK and exposure parameters for leuprorelin 1 mg IV QD were simulated using literature data exactly as in report FP01C-13-001, which was assessed during the MAA of Camcevi 42 mg. Exposure parameters for Lupron 1 mg IV QD, Camcevi 21 mg SC Q3M, and Camcevi 42 mg SC Q6M are summarized in Table 14.

Table 7. Leuprorelin Exposure (Geometric Mean (%CV)) at Steady-State for Lupron 1 mg, Camcevi 21 mg, and Camcevi 42 mg.

Treatment	AUC0-24h (ng. h/mL)	AUC0-6mo (ng. h/mL)	Cmax (ng/mL)	Css [b] (ng/mL)	Swing (Cmax-Cmin)/Cmin	Leuprorelin [e] (mg)
Lupron 1 mg	147 (14.8)	24696 (14.8) [a]	116 (33.6)	6.11 (14.8)	1932	157
Camcevi 21 mg	525 (49.1)	4854 (56.8) [d]	43.4 (43.1)	0.92 (71.7)	189 [c]	42
Camcevi 42 mg	975 (64.1)	6611 (36.9)	79.5 (74.0)	1.30 (38.2)	180 [c]	42

Exposure parameters for Camcevi 42 mg are observed data from study FP01C-13-001.
[a] Extrapolated from $AUC_{0\text{-}24h}$ using the formula: $AUC_{0\text{-}24h} \times 168$ days.
[b] C_{ss} Lupron = $AUC_{0\text{-}24h}/24$; C_{ss} LMIS 25 mg = $AUC_{(\text{after burst phase, set to 72-2016 h})}/(2016\text{-}72)$;
C_{ss} Camcevi 42 mg = $AUC_{(\text{after burst phase, set to 72-4032 h})}/(4032\text{-}72)$.
[c] Includes burst phase.
[d] Extrapolated from $AUC_{0\text{-}2016h}$ using the formula: $AUC_{0\text{-}2016h} \times 2$ doses.
[e] Leuprorelin free base equivalent.

FSEE-PMX-FP001-1605 was a cross-study PK comparison of Camcevi 42 mg and Camcevi 21 mg to four marketed leuprorelin acetate depot products. The report was evaluated during the MAA of Camcevi 42 mg. Relevant comparisons for the current line extension application are as follows:

- Camcevi 21 mg Q3M vs US-Eligard 22.5 mg Q3M. The Applicant provided supplementary information confirming that these PK data for US-Eligard 22.5 mg are applicable to EU-Eligard 22.5 mg.
- Camcevi 21 mg Q3M vs US-Lupron 22.5 mg Q3M
- Camcevi 42 mg Q6M vs EU-Lucrin 22.5 mg and 30 mg Q6M vs two consecutive injections of Camcevi 21 mg Q3M

PK parameters for Camcevi 42 mg and Camcevi 21 mg were obtained from clinical studies FP01C-13-001 and FP01C-17-001, respectively. Published data for Eligard, Lupron, and Lucrin were obtained from public sources, including public assessment reports by regulatory agencies. The data used for simulations for Eligard and Lupron are from FDA approval packages. Data for Lucrin is obtained from a public assessment report of Netherlands Medicines Evaluation Board.

Leuprorelin concentration-time curves for Camcevi 21 mg vs Eligard 22.5 mg and Camcevi 21 mg vs Lupron 22.5 mg are shown in Figure 1 and Figure 2, respectively, and concentration-time curves for two consecutive injections of Camcevi 21 mg vs single injection of Camcevi 42 mg, Lucrin 22.5 mg, and Lucrin 30 mg are shown in Figure 3. Mean exposure parameters are summarised in Table 15 to Table 17.

Figure 1. Mean (±SE) serum leuprolide profiles after two injections of Camcevi 21 mg (LMIS 25 mg) or Eligard 22.5 mg Q3M.

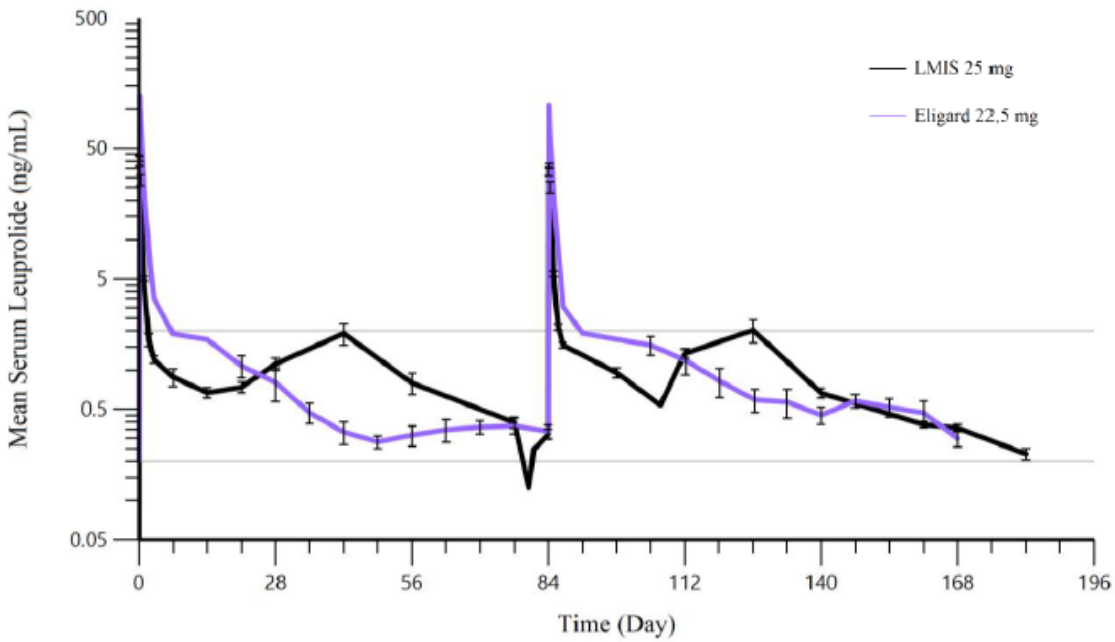


Table 8. Mean Exposure Parameters of Camcevi 21 mg (LMIS 25 mg) Q3M and Eligard 22.5 mg Q3M

Treatment	Cmax (ng/mL)	Tmax (h)	Cwk4 (ng/mL)	Cwk12 (ng/mL)	AUC0-4wks (day*ng/mL)	AUC4-12wks (day*ng/mL)	AUC0-12wks (day*ng/mL)
Eligard 22.5 mg First Dose	126.8	4	0.8052	0.340	124.166	21.327	145.493
Camcevi 21 mg First Dose	39.00	3.781	1.119	0.3176	42.55	39.74	82.29
Eligard 22.5 mg Second dose	107.1	4	1.186	0.300	115.017	33.020	148.036
Camcevi 21 mg Second Dose	37.73	3.859	1.332	0.3602	51.98	40.29	92.27

Figure 2. Mean serum leuprolide concentration after a single injection of Camcevi 21 mg (LMIS 25 mg) or Lupron 22.5 mg

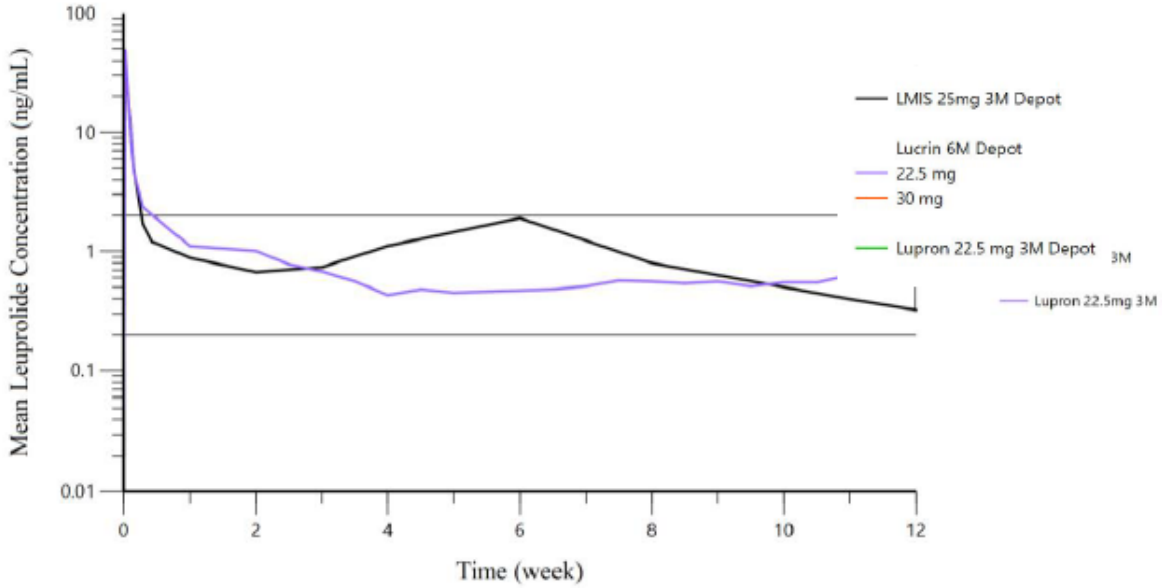


Table 9. Mean exposure parameters after single doses of Camcevi 21 mg or Lupron 22.5 mg.

Study	Product	AUC0-4wks (h*ng/mL)	AUC0-12wks (h*ng/mL)	AUC4-12wks (h*ng/mL)	Cmax (ng/mL)	Tmax (h)	C4wks (ng/mL)	C12wks (ng/mL)
M91-582	Lupron 22.5 mg	1160	1870	705	48.8	4	0.43	0.58
FP01C - 17-001	Camcevi 21 mg	1130	2090	950	38.4	3.82	1.23	0.339

Figure 3. Serum Leuprolide Concentrations after 2 Consecutive Injections of Camcevi 21 mg (LMIS 25 mg) Q3M vs Camcevi 42 mg (LMIS 50 mg), Lucrin 22.5 mg, and Lucrin 30 mg Q6M.

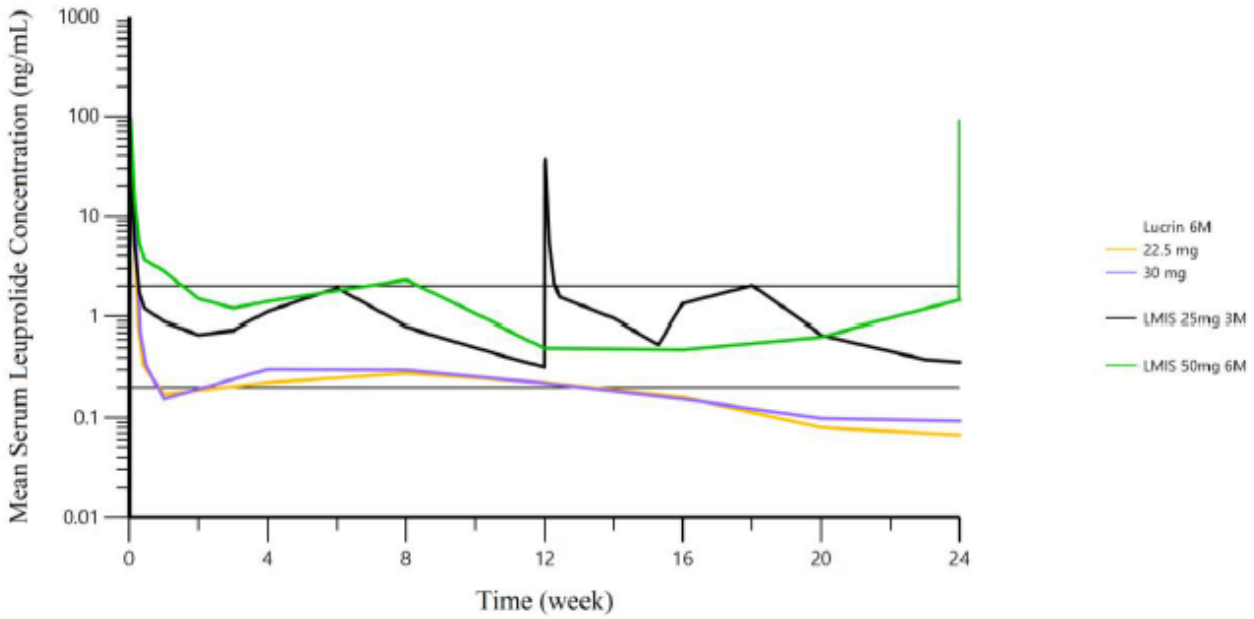


Table 10. Mean exposure parameters of after a single dose of Camcevi 42 mg Q6M, Lucrin 22.5/30 mg Q6M, and two doses of Camcevi 21 mg Q3M formulations.

Study	Product	$AUC_{0\text{-}4wks}$ (h*ng/mL)	$AUC_{4\text{-}24wks}$ (h*ng/mL)	C_{max} (ng/mL)	T_{max} (h)
EC 403 (Responders*)	Lucrin 22.5 mg Q6M	965	593	88.6	1.88
EC 403 (Responders*)	Lucrin 30 mg Q6M	1250	650	98.4	1.94
FP01C-17-001	Camcevi 21 mg Q3M (two doses)	2260	1410	38.4	4.00
FP01C-13-001	Camcevi 42 mg Q6M	2750	2950	96.7	3.61

* Responders: Patients without two consecutive elevations of testosterone greater than the castration level (>0.5 ng/mL).

5.2.2.2.1. Population Pharmacokinetics

N/A

5.2.2.2.2. Physiology based pharmacokinetic model

N/A

5.2.2.3. Absorption

After leuprorelin dosing, an initial rapid increase of serum leuprorelin concentration are observed, followed by a rapid decline over the first 3 days post-dose. The PK profile of Camcevi 21 mg as determined in main Study FP01C-17-001 exhibited two phases characterized by a distinctive burst phase and a plateau phase between the leuprorelin concentration and time. After the initial burst phase characterized by mean high serum concentrations (> 34 ng/mL), mean serum leuprorelin levels maintained relatively constant over most of each 12-week (approximately 3-month) dosing interval. Leuprorelin appeared to be released continuously by the third day after dosing, with steady serum concentrations ("plateau" phase) through the

12-week (approximately 3-month) dosing interval (mean concentration in study Part II: 0.30 - 1.59 ng/mL).

Mean leuprorelin serum concentration-time profiles were similar after the first and second dose. The serum leuprorelin concentrations and the associated PK following the first and second doses of Camcevi 21 mg suggested lack of significant accumulation with repeated dosing at 12 week intervals.

5.2.2.4. Bioequivalence

Bioequivalence of Camcevi 21 mg has not been directly compered against other leuprorelin products and no bioequivalence study has been presented in the current documentation.

5.2.2.5. Distribution

The distribution of leuprorelin after subcutaneous administration of Camcevi 21 mg has not been investigated in the current documentation. The mean steady-state volume of distribution of leuprorelin following intravenous bolus administration to healthy male volunteers was 27 liters. *In vitro* binding to human plasma proteins ranged from 43% to 49%. (Eligard SmPC 2022)

5.2.2.6. Metabolism

No dedicated clinical study on the metabolism of leuprorelin with administration of Camcevi 21 mg has been conducted and no drug metabolism study was conducted with leuprorelin acetate depot formulations (e.g., Eligard 45 mg) (SmPC Eligard, 2019). The major metabolite of leuprorelin is a pentapeptide (M-I) metabolite (Product Monograph Eligard, 2018).

5.2.2.7. Elimination

The elimination and excretion of leuprorelin after subcutaneous administration of Camcevi 21 mg has not been specifically investigated.

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 3 hours based on a two compartment model (Eligard SmPC 2022)

5.2.2.8. Dose proportionality and time dependency

Dose proportionality and time dependency has not been formally investigated for Camcevi 21 mg.

5.2.2.9. Pharmacokinetics in the target population

An open-label, single-arm, multi-national, multi-centre study was performed to assess the safety, efficacy, and pharmacokinetic behaviour of Camcevi 21 mg (LMIS 25 mg) in patients with prostate cancer (n=144, one drop out) (Study FP01C-17-001). Subjects received 2 separate doses of Camcevi 21 mg (equivalent to 21 mg leuprorelin) by subcutaneous injection at 12 weeks apart. See Section on Clinical Efficacy of this AR for details of the study design.

PK of leuprorelin were followed after the two SC injections of Camcevi 21 mg. For the first 30 subjects (PK Population 1) PK samples were collected on Day 0 prior the first dose and at 2, 4 and 8 hours post-dose, Days 1, 2, 3, 7, 14, 21, 28, 56, 77, 84 (Week 12: prior to the second dose and at 2, 4 and 8 hours post

the second dose), Days 85, 86, 87, 98, 112, 140, 161, 168 (week 24) and 182 (week 26, EOS). For the remaining subjects (PK Population 2) PK samples were collected on Day 0 (prior to the first dose of Camcevi 21 mg, and 4 hours post-dose), Days 1, 3, 14, 21, 28, 56, 77, 84 (Week 12: prior to the second dose and 4 hours post-dose), 85, 86, 87, 98, 112, 140, 161, and 168 (week 24/EOS). Serum leuprorelin levels were analysed using a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) method and the PK parameters were assessed using non-compartmental methods.

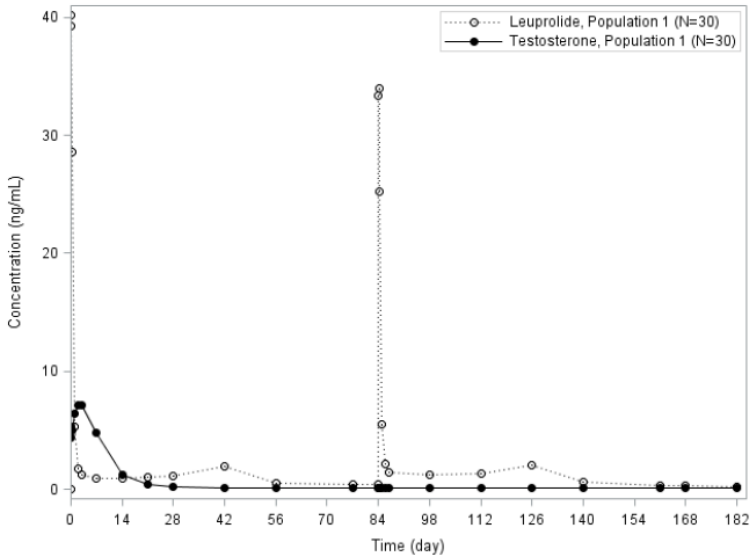
The serum pharmacokinetic profile of leuprorelin were evaluated after the two separate doses of Camcevi 21 mg and the first enrolled 30 subjects were considered as a subset for PK assessment and were followed for an additional 2 weeks (Day 182/week 26) post Day 168 (week 24) to establish the extended PK and PD profiles of serum leuprorelin and testosterone levels. The PK parameters of leuprorelin were determined during the study period, including C_{max}, T_{max}, C_{week4}, C_{week12}, $AUC_{0\text{-}week4}$, $AUC_{0\text{-}week12}$, $C_{avg(0\text{-}week12)}$ after each dose. In addition, PD analysis (serum testosterone and leuprorelin levels) were performed in the first enrolled 30 subjects on Day 182 (week 26).

Results

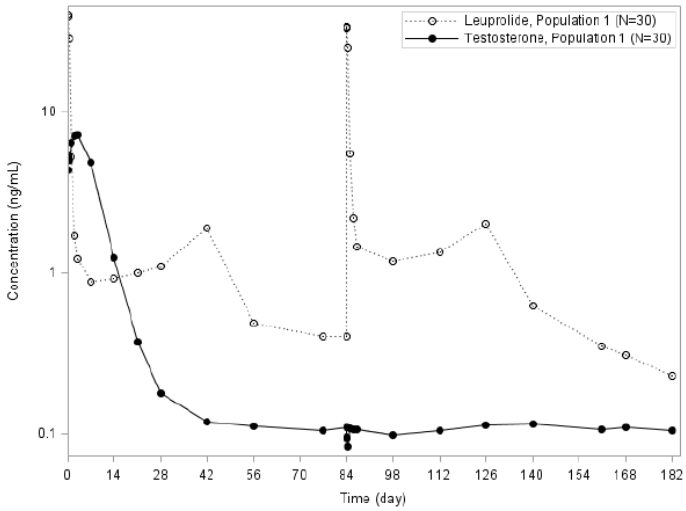
The formulation of Camcevi 21 mg resulted in a two-phase leuprorelin concentration versus time profiles characterized by a distinctive burst and a plateau phase. After dosing, an initial rapid increase of serum leuprorelin concentration was observed, followed by a rapid decline over the first 3 days postdose. (Figure 4 & Figure 5)

Figure 4: Arithmetic Mean Leuprorelin and Testosterone Serum Concentration-Time after Camcevi 21 mg (LMIS 25 mg) SC Injections to Male Subjects with Prostate Cancer in PK Population 1

Linear Scale



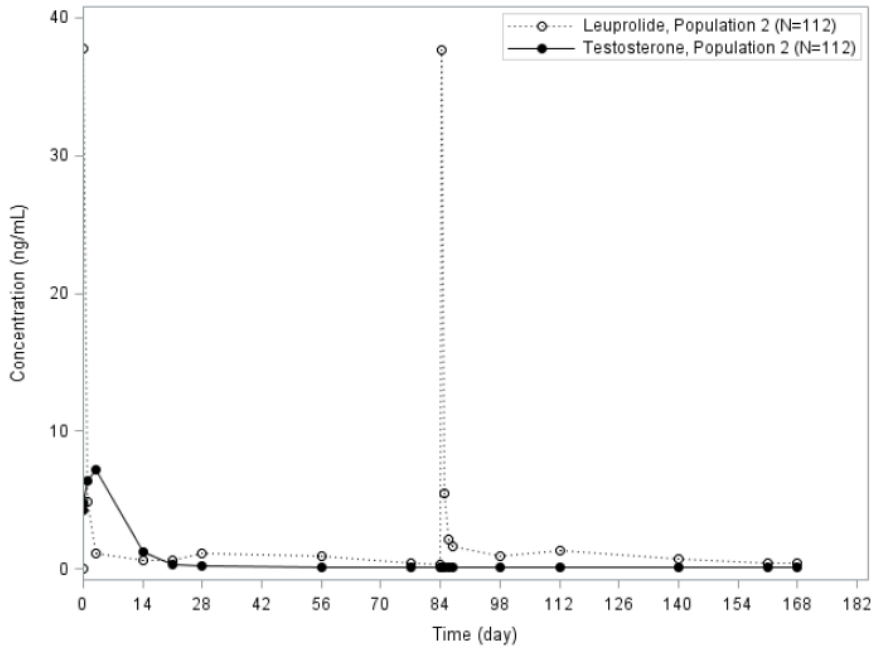
Log Scale



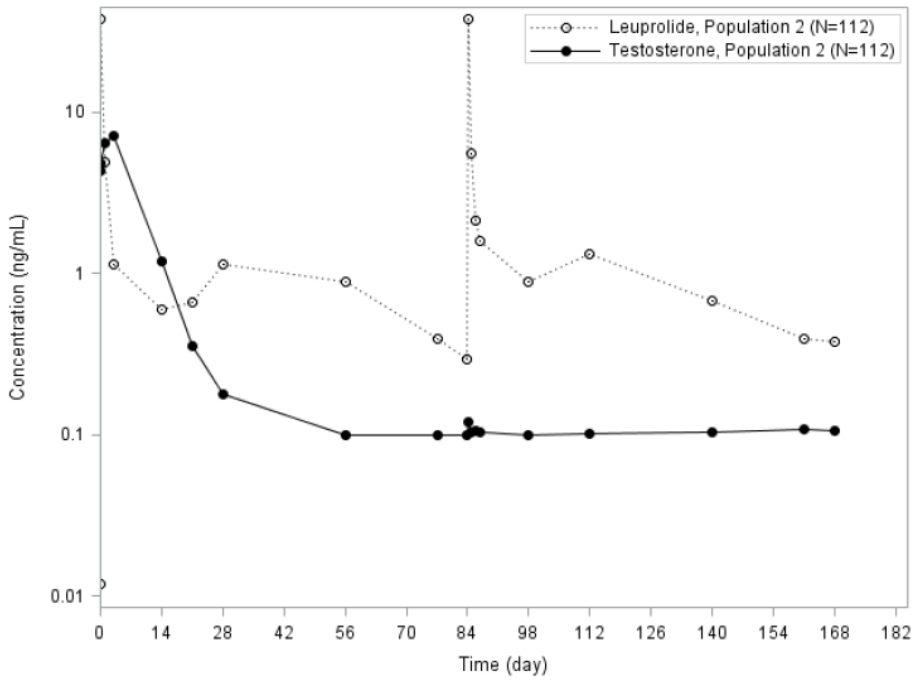
*Subject LT02-002 withdrew from the study on Day 112, so data of only 29 subjects were collected after Day 112.

Figure 5: Arithmetic Mean Leuprorelin and Testosterone Serum Concentration-Time after Camcevi 21 mg (LMIS 25 mg) SC Injections to Male Subjects with Prostate Cancer in Population 2

Linear Scale



Log Scale



Leuprorelin appeared to be released continuously by the third day after dosing, with steady serum concentrations ("plateau" phase) through the 12-week dosing interval (mean concentration in Population 2: 0.30 – 1.59 ng/mL). The mean C_{max} of serum leuprorelin was around 37.7-43.4 ng/mL and it reached maximal level approximately 2~4 hours after the first and the second dose of Camcevi 21 mg injections. The mean concentration of leuprorelin then declined to 0.30 to 0.40 ng/mL at 12 weeks (C_{week12}). The

serum leuprorelin concentrations and the associated exposure parameters following the first and second doses of Camcevi 21 mg were similar.

The PK parameters are presented for the first enrolled 30 subjects (PK population 1) which measured the serum PK profile of leuprorelin for up to 26 weeks following 2 subcutaneous injections of Camcevi 21 mg (Table 18), and the remaining subjects (PK population 2), which measured the serum pharmacokinetic profile of leuprorelin for up to 24 weeks.

Table 11: PK Parameters of Camcevi 21 mg in PK population 1 (PK subset) and PK population 2

PK Population 1 (PK sub-set)						
PK Parameter	**First Dose**			**Second Dose**		
	N	**Mean**	**SD**	**N**	**Mean**	**SD**
C_{max}, ng/mL	30	43.4	18.7	30	37.8	14.9
T_{max}, h	30	2.00 (2.00, 8.00)		30	2.00 (1.92, 8.00)	
C_{week4}, ng/mL	30	1.09	1.45	30	1.35	1.29
C_{week12}, ng/mL	30	0.400	0.534	29 [a]	0.309	0.164
C_{last}, ng/mL*	NA			29 [a]	0.228	0.126
$AUC_{0\text{-}week4}$, day·ng/mL	30	48.2	29.6	30	53.9	32.3
$AUC_{0\text{-}week12}$, day·ng/mL	30	93.5	50.4	30	102	45.3
$C_{avg(0\text{-}week12)}$, ng/mL	30	1.11	0.600	30	1.22	0.539
T_{max}: Median (Min, Max); *: C_{last} is listed under the second dose only; NA; not applicable. a: not reportable for 1 subject (LT02-002)						
PK Population 2						
PK Parameter	**First Dose**			**Second Dose⁑**		
	N	**Mean**	**SD**	**N**	**Mean**	**SD**
C_{max}, ng/mL	111 [b]	37.8	17.7	101 [e]	37.7	20.0
T_{max}, h	111 [b]	4.00 (3.00, 4.42)		101 [e]	4.00 (3.52, 4.25)	
C_{week4}, ng/mL	111 [b]	1.13	1.45	102	1.33	1.20
C_{week12}, ng/mL	109 [d]	0.295	0.250	100 [f]	0.375	0.277
$AUC_{0\text{-}week4}$, day·ng/mL	111 [b]	41.0	17.6	100 [f]	51.4	24.1
$AUC_{0\text{-}week12}$, day·ng/mL	110 [c]	79.2	43.4	100 [f]	89.2	36.9
$C_{avg(0\text{-}week12)}$, ng/mL	110 [c]	0.943	0.516	100 [f]	1.06	0.439
Tmax: Median (Min, Max); *: Clast is listed under the second dose only; NA; not applicable. b: not reportable for 1 subject (LT01-006); c: not reportable for 2 subjects (LT01-006, LT04-022); d: not reportable for 3 subjects (KR02-004, LT04-022, SK02-026); e: not reportable for 1 subject (CZ03-004); f: not reportable for 2 subjects (CZ03-004, KR02-007); ⁑ CZ03-007, CZ03-008, CZ03-009, CZ03-012, and CZ03-013 withdraw from the study due to site close before the second dose; KR02-004, LT03-006, LT04-022, SK02-026, and SK02-028 withdraw from the study with withdrew consent before the second dose.						

5.2.2.10. Special populations

Impaired renal function

The PK characteristics of leuprorelin following Camcevi 21 mg in renally impaired patients have not been determined.

Impaired hepatic function

The PK characteristics of leuprorelin following Camcevi 21 mg in hepatically impaired patients have not been determined.

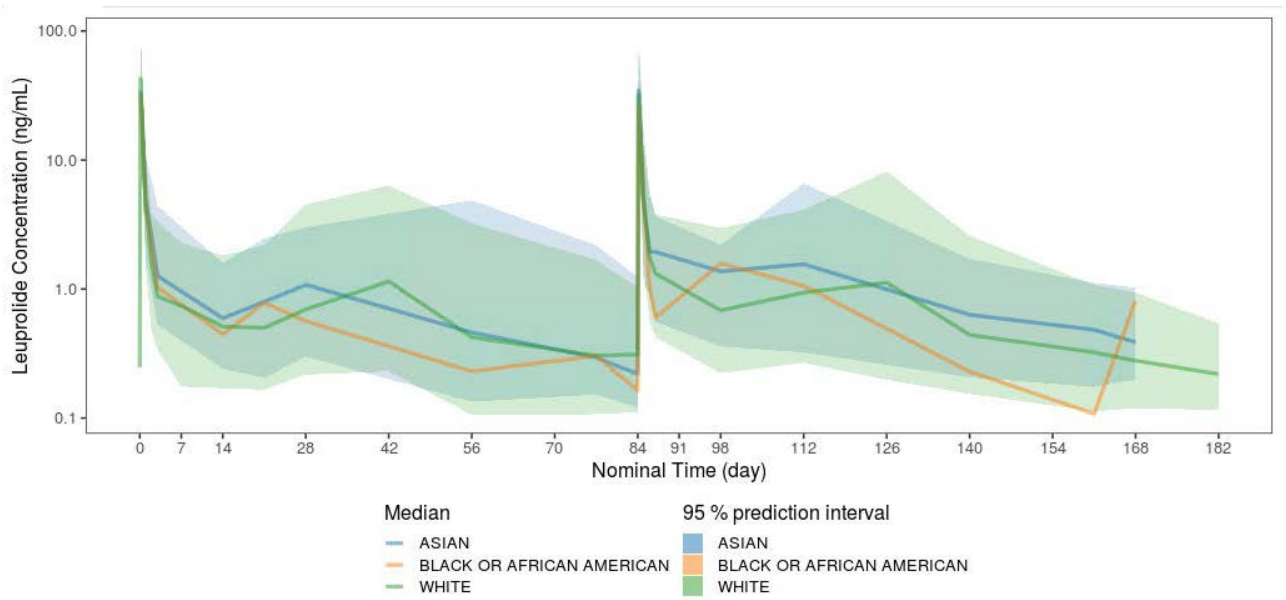
Gender

No investigations have been conducted with Camcevi 21 mg in women. As a drug intended for use in prostatic cancer, Camcevi 21 mg is not indicated for use in women.

Race

Similar serum leuprorelin median profiles were observed over the 2 dosing periods for White (n=127), Black or African American (n=1) (Total Non Asian population n=128) and Asian (n=16) race groups (Figure 6). No significant differences were observed (p values all >0.1). Overall, similar serum leuprorelin median profiles were observed over the 2 dosing periods for Asian vs non-Asian race groups. Except for differences in peak leuprorelin concentration between Asian and White (p value <0.05), there were no statistically significant differences in PK parameters between Asian and other races (all p values >0.20).

Figure 6: Median (95% prediction interval) Serum Leuprorelin Concentration vs. Time After a Single SC Dose of Camcevi 21 mg (LMIS 25 mg) (Day 0) or Multiple SC Dose of Camcevi 21 mg (LMIS 25 mg) (Day 84) by Race [Semi-Log Scale]



Weight

Across body weight categories, overall peak concentrations of serum leuprorelin were decreased by 35% in subjects >100 kg compared to subjects <75 kg. (Figure 7)

Comparing subjects with body weight of <75 kg vs >100 kg, overall serum leuprorelin exposure over the first 4 weeks ($AUC_{0\text{-}4wks}$) following Camcevi 21 mg administration was lower by 44% (geometric mean 53.9 vs 30.1 ng·day/mL, respectively), while exposure over the first 12 weeks ($AUC_{0\text{-}12wks}$) was lower by 34% (geometric mean 95.3 vs 62.7 ng·day/mL, respectively).

Significant differences related to subject's body weight were observed for serum leuprorelin peak concentration, average concentration and exposure (when including all body weight categories) following 4 and 12 weeks after dosing with p values ≤ 0.001. Subjects with body weight of >100 kg will have their serum leuprorelin exposure (C_{max} and $AUC_{0\text{-}4wks}$) decreased by approximately 35 and 44%, respectively, compared to subjects with a body weight of 60 kg. (Table 19)

Figure 7: Median Serum Leuprorelin Concentration vs. Time After a Single SC Dose of Camcevi 21 mg (LMIS 25 mg) (Day 0) or Multiple SC Dose of Camcevi 21 mg (LMIS 25 mg) (Day 84) by Body Weight Categories (kg) [Semi-Log Scale]

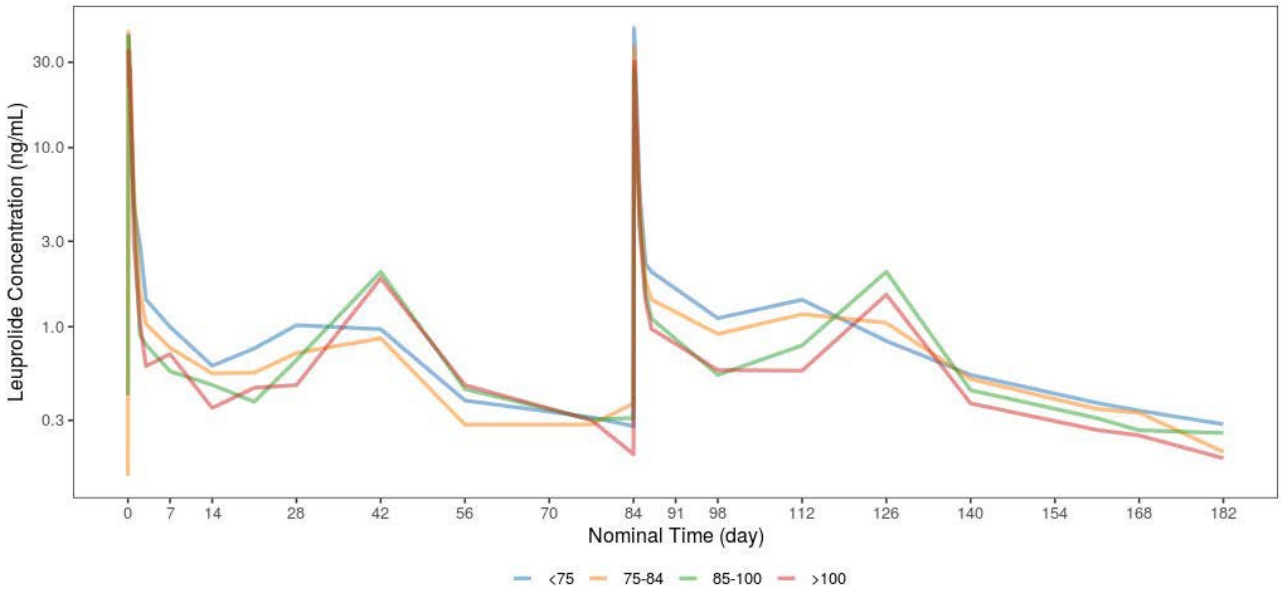


Table 12: Serum Leuprorelin Pharmacokinetic Parameters by Body Weight Categories (Overall)

Body Weight Categories	<75kg (n=69)	75-84kg (n=64)	85-100kg (n=100)	>100kg (n=39)	Overall (n=272)
Cmax (ng/mL)					
Geo. Mean (Geo. CV%)	39.7 (48.3)	37.3 (55.4)	32.3 (49.5)	25.8 (54.4)	34.1 (53.5)
Median [Min, Max]	39.9 [9.28, 95.4]	39.3 [11.5, 90.5]	33.5 [11.4, 84.4]	24.8 [5.39, 70.9]	33.9 [5.39, 95.4]
Tmax (h)					
Median [Min, Max]	4.00 [2.00, 4.42]	4.00 [1.92, 8.00]	4.00 [2.00, 4.25]	4.00 [2.00, 8.00]	4.00 [1.92, 8.00]
Cavg(0-12wk) (ng/mL)					
Geo. Mean (Geo. CV%)	1.13 (40.7)	1.01 (37.8)	0.867 (44.4)	0.746 (50.4)	0.941 (45.4)
Median [Min, Max]	1.09 [0.424, 2.68]	1.00 [0.358, 2.07]	0.845 [0.409, 4.51]	0.686 [0.313, 2.05]	0.952 [0.313, 4.51]
Missing	0 (0%)	1 (1.6%)	1 (1.0%)	0 (0%)	2 (0.7%)
AUC0-4wks (ng·day/mL)					
Geo. Mean (Geo. CV%)	53.9 (46.0)	47.5 (44.5)	37.0 (47.4)	30.1 (48.7)	41.9 (51.5)
Median [Min, Max]	53.1 [24.7, 171]	49.4 [17.6, 102]	38.3 [12.8, 166]	29.0 [10.1, 67.5]	42.5 [10.1, 171]
Missing	0 (0%)	1 (1.6%)	0 (0%)	0 (0%)	1 (0.4%)
AUC0-12wk (ng·day/mL)					
Geo. Mean (Geo. CV%)	95.3 (40.7)	84.5 (37.8)	72.8 (44.4)	62.7 (50.4)	79.0 (45.4)
Median [Min, Max]	91.5 [35.6, 225]	84.4 [30.1, 174]	71.0 [34.3, 379]	57.7 [26.3, 172]	80.0 [26.3, 379]
Missing	0 (0%)	1 (1.6%)	1 (1.0%)	0 (0%)	2 (0.7%)
Cwk12 (ng/mL)					
Geo. Mean (Geo. CV%)	1.20 (97.9)	0.978 (77.7)	0.752 (87.9)	NA (NA)	NA (NA)
Median [Min, Max]	1.31 [0.270, 12.7]	1.05 [0.266, 3.61]	0.688 [0.104, 5.35]	0.489 [0.00, 8.15]	0.837 [0.00, 12.7]
Missing	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
Cwk4 (ng/mL)					
Geo. Mean (Geo. CV%)	NA (NA)	NA (NA)	NA (NA)	NA (NA)	NA (NA)
Median [Min, Max]	0.291 [0.00, 2.87]	0.345 [0.00, 1.24]	0.261 [0.00, 1.15]	0.198 [0.00, 0.757]	0.270 [0.00, 2.87]
Missing	2 (2.9%)	1 (1.6%)	2 (2.0%)	1 (2.6%)	6 (2.2%)

Age

Across age categories, peak concentration of serum leuprorelin was increased 1.8-fold in subjects aged > 79 years compared to subjects aged < 60 years. Total serum leuprorelin exposure was also increased with age, as a 2-fold increase was observed at 3 months following Camcevi 21 mg administration in subjects aged > 79 years compared to subjects < 60 years. The relationship between serum leuprorelin PK parameters and age was statistically significant ($p \leq 0.001$). (Figure 8 & Table 20)

Figure 8: Median Serum Leuprorelin Concentration vs. Time After a Single SC Dose of Camcevi 21 mg (LMIS 25 mg) (Day 0) or Multiple SC Dose of LMIS 25 mg (Day 84) by Age Categories [Semi-Log Scale]

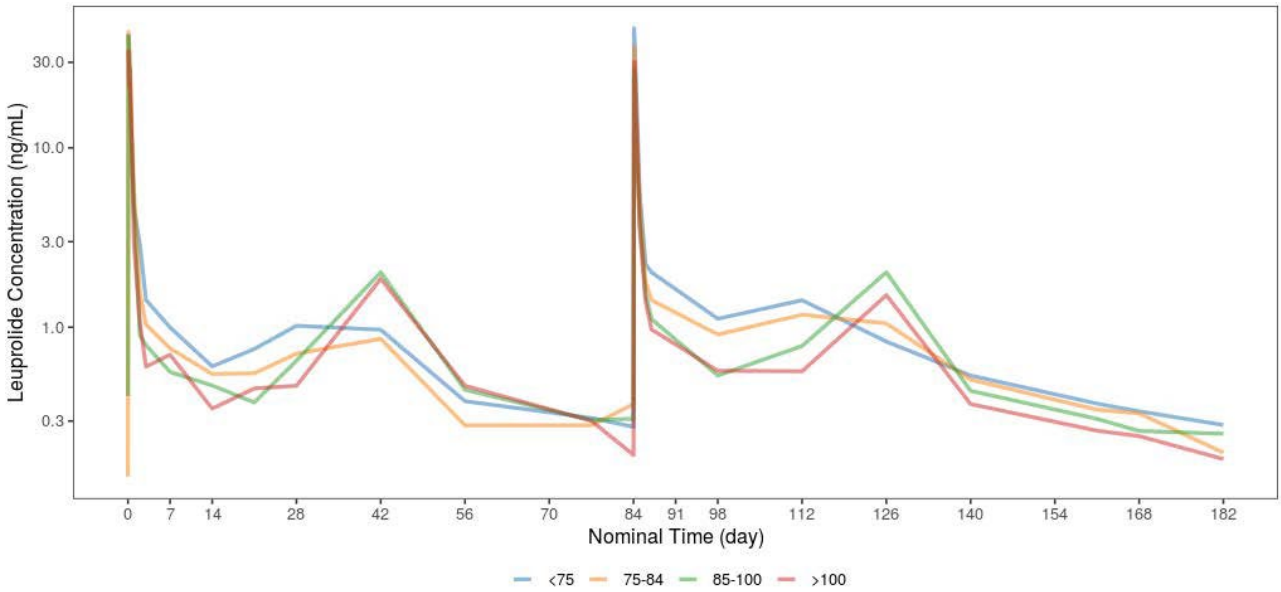


Table 13: Serum Leuprorelin Pharmacokinetic Parameters by Age Groups (Overall)

	Age Groups (years)				
	<60 (n=26)	**60-69 (n=110)**	**70-79 (n=108)**	**>79 (n=28)**	**Overall (n=272)**
Cmax (ng/mL)					
Geo. Mean (Geo. CV%)	30.9 (53.7)	32.3 (49.5)	35.2 (54.8)	41.0 (59.6)	34.1 (53.5)
Median [Min, Max]	32.9 [11.4, 79.6]	33.3 [11.3, 94.6]	34.8 [5.39, 95.4]	52.0 [11.5, 83.3]	33.9 [5.39, 95.4]
Tmax (h)					
Median [Min, Max]	4.00 [2.00, 4.00]	4.00 [2.00, 8.00]	4.00 [1.92, 8.00]	4.00 [3.92, 4.23]	4.00 [1.92, 8.00]
Cavg(0-12wk) (ng/mL)					
Geo. Mean (Geo. CV%)	0.684 (35.4)	0.856 (46.1)	1.04 (39.1)	1.24 (43.6)	0.941 (45.4)
Median [Min, Max]	0.679 [0.350, 1.19]	0.886 [0.313, 4.51]	1.04 [0.358, 2.51]	1.21 [0.613, 2.68]	0.952 [0.313, 4.51]
Missing	0 (0%)	0 (0%)	2 (1.9%)	0 (0%)	2 (0.7%)
AUC0-4wks (ng·day/mL)					
Geo. Mean (Geo. CV%)	31.7 (54.1)	36.9 (47.7)	47.0 (46.2)	57.6 (51.1)	41.9 (51.5)
Median [Min, Max]	33.5 [14.4, 72.2]	36.7 [10.1, 166]	48.4 [12.8, 105]	55.3 [28.8, 171]	42.5 [10.1, 171]
Missing	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	1 (0.4%)
AUC0-12wk (ng·day/mL)					
Geo. Mean (Geo. CV%)	57.4 (35.4)	71.9 (46.1)	87.7 (39.1)	104 (43.6)	79.0 (45.4)
Median [Min, Max]	57.1 [29.4, 100]	74.4 [26.3, 379]	87.8 [30.1, 211]	101 [51.5, 225]	80.0 [26.3, 379]
Missing	0 (0%)	0 (0%)	2 (1.9%)	0 (0%)	2 (0.7%)
Cwk4 (ng/mL)					
Geo. Mean (Geo. CV%)	0.470 (81.6)	NA (NA)	1.08 (90.4)	1.20 (88.6)	NA (NA)
Median [Min, Max]	0.416 [0.104, 1.95]	0.645 [0.00, 5.35]	1.04 [0.270, 12.7]	1.16 [0.274, 5.51]	0.837 [0.00, 12.7]
Missing	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	1 (0.4%)
Cwk12 (ng/mL)					
Geo. Mean (Geo. CV%)	NA (NA)	NA (NA)	NA (NA)	0.441 (77.0)	NA (NA)
Median [Min, Max]	0.197 [0.00, 0.532]	0.243 [0.00, 0.986]	0.316 [0.00, 1.76]	0.411 [0.144, 2.87]	0.270 [0.00, 2.87]
Missing	0 (0%)	0 (0%)	5 (4.6%)	1 (3.6%)	6 (2.2%)

Children

No investigations have been conducted with Camcevi 21 mg in paediatric populations. As drug intended for use in prostate cancer, Camcevi 21 mg is not indicated for use in children.

5.2.2.11. Pharmacokinetic interaction studies

5.2.2.11.1. Special populations

NA

5.2.2.11.2. PK drug-drug interactions

No specific drug-drug interaction studies have been carried out with leuprorelin following subcutaneous administration of Camcevi 21 mg.

5.2.2.11.3. Dose proportionality/time independence/accumulation

NA

5.2.3. Pharmacodynamics

5.2.3.1. Primary and secondary pharmacology

The Applicant has not performed new clinical studies addressing primary and secondary pharmacology.

Independent PD studies were not performed for the current line extension application since the PD of leuprorelin are known and several leuprorelin-containing products are available in EU. The phase 3 evidence of efficacy was based on PD biomarkers, primarily testosterone and secondarily on PSA and LH level measurements. For evaluation of these aspects, see 5.3. Clinical efficacy.

5.2.3.2. Pharmacodynamic interactions with other medicinal products or substances

The Applicant has not performed specific pharmacodynamic drug-drug interaction studies.

5.2.3.3. Genetic differences in PD response

The Applicant has not performed studies on genetic difference in PD response.

5.2.3.4. Immunological events

The Applicant has not performed studies on immunogenicity.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Various leuprorelin depot forms have been developed for use at different dosing intervals (monthly, 3-monthly, 4-monthly, 6-monthly). They are considered therapeutically similar in androgen deprivation therapy if the following key criteria are met: 1) Serum leuprorelin trough levels (C_{trough}) are kept within the

therapeutic range for effective serum testosterone suppression, and 2) There is no excess in leuprorelin exposure and leuprorelin release characteristics over time are reliable. Data not shown.

No exposure-response or dose-response modelling was conducted by the Applicant to support the current application.

5.2.5. Dose selection and therapeutic window

Camcevi 21 mg (administered SC Q3M) was developed to provide an alternative option to Camcevi 42 mg (administered SC Q6M). Prospective PK/PD modelling was not conducted for dose selection. *Post hoc* analyses were conducted to compare observed leuprorelin exposure following Camcevi 21 mg SC Q3M regimen with exposure levels reported for other leuprorelin products, including Camcevi 42 mg SC Q6M; see Clinical efficacy section of this AR.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

Bioanalytical methods

Three bioanalytical methods were used for the determination of leuprorelin, testosterone and luteinising hormone in serum samples from clinical studies. LC-MS/MS bioanalytical methods were used for the determination of the concentration of leuprorelin and testosterone in human serum. For the determination of luteinising hormone in human serum a commercial chemiluminescense ELISA method was used. The analytical methods are acceptable and properly validated, the same methods were also utilised for Camcevi 42 mg. The performance of the bioanalytical methods was satisfactory during the sample analysis and the handling of the samples was adequate.

Pharmacokinetics

Pharmacokinetics of Camcevi 21 mg has been studied in one Phase 3 clinical study (FP01C-17-001). 144 patients with advanced prostate cancer were enrolled in a single multicenter study where Camcevi 21 mg was administered as a subcutaneous injection in two separate occasions three months apart from each other. Serum leuprorelin levels were followed up to 26 weeks (182 days) for the first 30 enrolled patients (PK population 1) and for the remaining patients (PK population 2) sampling was performed up to 24 weeks (168 days).

Leuprorelin concentration time profiles were characterized by two phases. An initial rapid increase was seen after Camcevi 21 mg injection followed by a rapid decline over the first 3 days post-dose. Thereafter leuprorelin was released steadily and serum concentrations remained rather constant over the 12 weeks dosing interval. The mean C_{max} of serum leuprorelin was around 37.7-43.4 ng/mL and it reached maximum approximately 2-4 hours after injection. Mean concentration of leuprorelin was about 0.30-0.40 ng/mL at the end of the dosing interval (week 12) and the concentrations and pharmacokinetic parameters were similar after the first and second doses of Camcevi 21 mg. Leuprorelin concentrations and PK parameters were also similar in the two PK population groups (PK populations 1 and 2).

Leuprorelin exposure (AUC) was about 34% lower in patients >100 kg compared to those <75 kg. Leuprorelin exposure also increased with age. A 1.8-fold increase was seen in subjects >79 years (n=28) compared to patients <60 years (n=26). Race was found to not affect pharmacokinetics of leuprorelin but this result is tentative due to small number of non-Caucasian patients in the dataset (White/Caucasian n=127; Black/African American n=1; Asian n=16. In the Phase 3 study (FP01C-17-001) the dose was not

adjusted by weight, age or race; dose adjustment by these factors is not proposed in the product information, which is acceptable and in agreement with Camcevi 42 mg.

The PK of leuprorelin after Camcevi 21 mg is well characterized. Cross-study PK comparison (FSEE-PMX-1605) indicated similar PK characteristics following SC injections of Camcevi 21 mg and US-Eligard 22.5 mg, which is applicable also to EU-Eligard 22.5 mg.

Pharmacodynamics

Pharmacodynamics (serum testosterone and luteinizing hormone (LH) concentrations) were the primary and secondary endpoints of study FP01C-17-001. See section 6.3 of this AR. Additional studies evaluating mechanism of action and primary/secondary PD were not conducted and are not required for this MAA for line extension of Camcevi 21 mg.

Exposure-response

Pharmacokinetics and pharmacodynamics were evaluated separately. No exposure-response analyses were conducted and none are required for assessment of benefit/risk.

5.2.6.2. Conclusions

The presented Clinical Pharmacology information supports the MAA for Camcevi 21 mg.

5.3. Clinical efficacy

5.3.1. Dose response study(ies)

No dose-response studies were performed and are not deemed necessary in this hybrid application, which is based on bridging to the reference product (Eligard 22.5 mg).

5.3.2. Main study(ies)

5.3.2.1. FP01C-17-001

5.3.2.1.1. Study title

An Open-Label, Single-Arm Study of the Efficacy, Safety, and Pharmacokinetic Behavior of Leuprolide Mesylate Injectable Suspension (LMIS 25 mg) in Subjects with Prostate Cancer

5.3.2.1.2. Study design

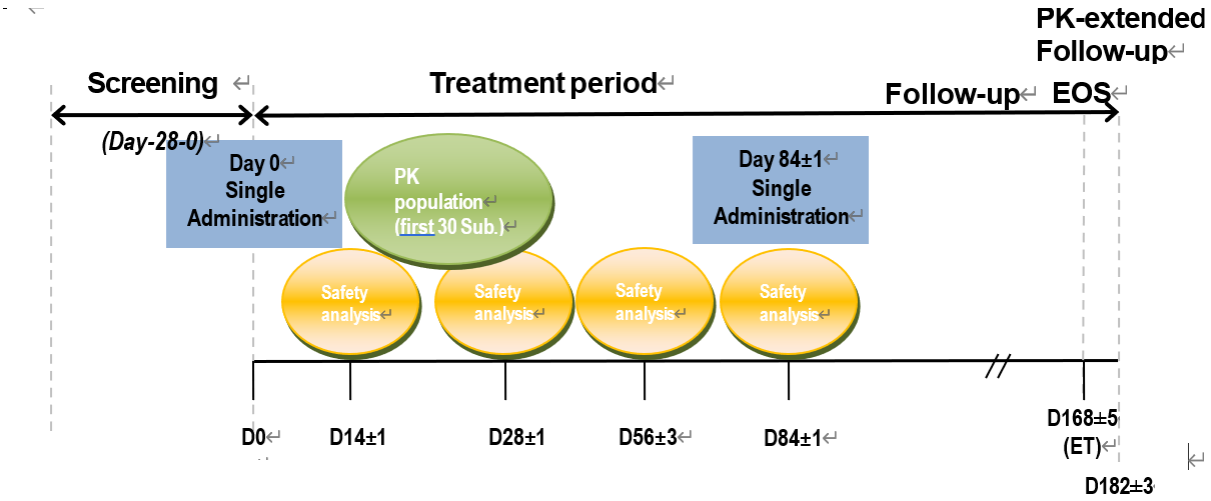
The study providing efficacy results is the Phase 3 study FP01C-17-001 on Camcevi 21 mg (Figure 9).This is a completed pivotal Phase 3, uncontrolled, multicentre, open-label, single-arm, 6-month, PK, safety and PD/efficacy study conducted in 144 males with prostate carcinoma in need for androgen deprivation therapy (male adult subjects with histologically confirmed prostate carcinoma, baseline morning serum testosterone level > 150 ng/dL, ECOG performance status ≤ 2, and with a life expectancy of at least 18 months).

Camcevi 21 mg was administered on Day 0 (Visit 2) and Day 84 (Visit 13). At the end of 12 weeks (Day 84), all subjects who had tolerated Camcevi 21 mg were administered the second dose of Camcevi 21 mg

and were followed for tolerability, safety, efficacy, PK/PD parameters for another 12 weeks (Day 168/week 24). No interim analyses were performed.

The study was conducted in Czech Republic, Lithuania, Slovakia, South Korea, and the United States (Table 21). The duration of recruitment was approximately 10 months, and in total 186 patients were screened.

Figure 9: The study design for study FP01C-17-001



* The first 30 subjects had extended sampling time points on Day 182 (week 26) to establish the full PK/PD profile of serum leuprolide

Table 14: Description of clinical efficacy (study FP01C-17-001)

Study features	In FP01C-17-001
Study ID	FP01C-17-001
Number of study centers	21[a]
Location(s)	Czech Republic, Lithuania, Slovakia, South Korea, United States
Design, control type	Open-label, single-arm
Study start	26-Sep-2017
Enrolment status, data	Completed 19-Nov-2018
Total enrolment/ enrollment goal	144/133
Study & control drugs	Camcevi 21 mg, no control
Dose, route & regimen	2 SC injections of Camcevi 21 mg given at ~ 12 weeks apart
Study objective	Efficacy, Safety, and PK
Duration	28 weeks
Gender Male/Female	144/0
Median age (range)	70 (51, 89)
Inclusion criteria	Males ≥ 18 years old with histologically confirmed prostate carcinoma with baseline serum testosterone level > 150 ng/dL, adequate organ functions, ECOG performance score ≤ 2
Efficacy evaluation	• Percentage of subject with serum testosterone levels ≤ 50 ng/dL by Day 28 (± 1 day) • Percentage of subjects with serum testosterone levels ≤ 50 ng/dL from Day 28 through Day 168

[a]= Includes site CZ03 that was terminated early due to GCP violation
ECOG = Eastern Cooperative Oncology Group, GCP = Good Clinical Practice, PK = pharmacokinetics, SC = subcutaneous

5.3.2.1.2.1. Treatment

Patients enrolled in this open-label, phase 3 study received a single subcutaneous injection of Camcevi 21 mg, prefilled and supplied in one sterile syringe, ready-to-use, every 12 weeks (approximately 3 months; over the course of 2 doses on Day 1 and Day 84).

5.3.2.1.2.2. Randomisation

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

5.3.2.1.2.3. Blinding

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

5.3.2.1.2.4. Patient population

The study population consisted of 144 patients that were enrolled in the study. This is a multicentre phase 3 study FP01C-17-001 conducted in the hospitals of Czech Republic, Lithuania, Slovakia, South Korea, and the United States.

Inclusion criteria:

1. Males aged ≥ 18 years old
2. Males with histologically confirmed cancer of the prostate
3. Subjects who are judged by the attending physician and/or principal investigator to be a candidate for androgen ablation therapy
4. Baseline morning serum testosterone level > 150 ng/dL performed at screening visit
5. Eastern Cooperative Oncology Group (ECOG) Performance score ≤ 2
6. Life expectancy of at least 18 months
7. Laboratory values
    a. Absolute neutrophil count ≥ 1,500 cells/μL
    b. Platelets ≥ 100,000 cells/μL
    c. Haemoglobin ≥ 10 gm/dL
    d. Total bilirubin ≤ 1.5 × ULN
    e. AST (SGOT) ≤ 2.5 × ULN
    f. ALT (SGPT) ≤ 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. HbA1c ≤9.5%

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

l. Normal urinalysis results within:

i. RBCs ≤ 3 RBCs/hpf

ii. WBCs ≤ 5 WBCs/hpf

iii. Nitrate: negative

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

Exclusion criteria:

1. Receipt of chemotherapy, immunotherapy, cryotherapy, radiotherapy, or anti-androgen therapy concomitantly, or within 8 weeks prior to screening visit, for treatment of Cancer of the prostate. Radiation for pain control will be allowed during the study.
2. Receipt of any vaccination (including influenza) within 4 weeks of screening visit
3. History of blood donation within 2 months of screening visit
4. History of anaphylaxis to any LH-RH analogues
5. Receipt of any LH-RH suppressive therapy within 6 months of screening visit
6. Patients who were previously enrolled in the LMIS 50 mg study
7. Major surgery, including any prostatic surgery, within 4 weeks of screening visit
8. History and concomitant clinical and radiographic evidence of central nervous system/spinal cord metastases and subjects at risk for spinal cord compression
9. Clinical evidence of active urinary tract obstruction and subjects at risk for urinary obstruction
10. History of bilateral orchiectomy, adrenalectomy, or hypophysectomy
11. History or presence of hypogonadism, or receipt of exogenous testosterone supplementation within 6 months of screening visit
12. Clinically significant abnormal ECG and/or history of clinically significant cardiovascular disease as judged by the investigator
13. History of drug and/or alcohol abuse within 6 months of screening visit
14. Contraindication to leuprolide or an LH-RH agonist as indicated on package labeling
15. Use of 5-alpha reductase inhibitor within the last 6 months of screening visit
16. History or presence of insulin-dependent diabetes mellitus (Type I). Presence of well controlled diabetes mellitus Type II will be allowed if only oral hypoglycemic are required. Prostate cancer subjects with poor controlled diabetes mellitus with Hb1Ac > 9.5% or urine glycosuria > 1.0 g/dL should be excluded.
17. Use of systemic corticosteroids at a dose > 10 mg/d or anti-androgens
18. Use of any investigational agent within 4 weeks of screening visit
19. Use of any over-the-counter medication within 4 weeks of screening visit except for those listed in the permitted Concomitant Treatment section.

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

5.3.2.1.3. Objectives and estimands

5.3.2.1.3.1. Primary objective

The purpose of this study was to evaluate the safety, efficacy, and pharmacokinetic (PK) of Camcevi 21 mg in subjects with prostate cancer after two subcutaneous injections given 12 weeks apart (on Day 0 and Day 84).

The primary endpoint of efficacy was: The percentage of subjects with a serum testosterone concentration suppressed to castrate levels (≤ 50 ng/dL) on Day 28 ± 1 day (week 4) following the first injection of Camcevi 21 mg, and the proportion of subjects with serum testosterone suppression (≤ 50 ng/dL) from Day 28 ± 1 day (week 4) through Day 168 ± 5 days (week 24) until the end of the study.

5.3.2.1.3.2. Estimand for the primary objective

Table 15: Estimand for primary objective

Population	Two populations: Patients with prostate cancer who received at least one subcutaneous injection given 12 weeks apart (on Day 0 and Day 84) referred as ITT population in SAP Patients with prostate cancer who received two subcutaneous injections given 12 weeks apart (on Day 0 and Day 84) referred as PP population in SAP
Treatment condition	Subjects with prostate cancer
Endpoint (variable)	Serum testosterone concentration suppressed to castrate levels (≤ 50 ng/dL)
Population-level summary	The percentage of subjects with a serum testosterone concentration suppressed to castrate levels (≤ 50 ng/dL) on Day 28 ± 1 day (week 4) and on Day 168± 5 days (week 24)
Intercurrent events and strategy to handle them	
Not clearly defined	Not clearly defined
Not clearly defined	Not clearly defined

The above estimand definition is according to the assessors´ interpretation.

Statistical methods for estimation and sensitivity analysis on primary estimand<s>

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

The duration of time to reach a serum testosterone of >50 ng/dL was calculated from Day 28 to Day 168 or Day of Discontinuation. The duration of time to reach a serum testosterone of > 50 ng/dL was to be

summarized and presented as number of subjects with event (event number), percentage of subjects with event, suppression rate by day 168 along with 95% confidence interval, mean, median and 95% confidence interval for median. A positive outcome to the study was to be achieved if the lower 95% confidence interval bound for the response rate at Day 168 is greater than 90%.

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

The sensitivity analysis for primary efficacy endpoint was to be performed by excluding all subjects from site CZ03 due to GCP compliance issues at this site. These subjects were to be excluded from both ITT and PP populations as another analysis scenario (ITT excluding subjects from site CZ03, and PP excluding subjects from site CZ03) for sensitivity analysis.

5.3.2.1.3.3. Secondary objectives

The analyses of secondary endpoints were based on the following:

- The mean acute-on-chronic (surge) changes in testosterone and LH levels from just prior to the second injection through 14 days after the second injection of Camcevi 21 mg (Days 85-87, week 13; Day 98 [14 days post the second dose], week 14)

An 'acute-on-chronic' change was defined as a >25% increase in testosterone and LH levels compared to the testosterone and LH levels just prior to the second injection. The mean acute-on-chronic (surge) changes in testosterone and LH levels were to be analysed based on subset of subjects have an 'acute-on-chronic' change at Visit 14 (Day 85), Visit 15 (Day 86), Visit 16 (Day 87) and Visit 17 (Day 98). The mean acute-on-chronic (surge) changes in testosterone and LH levels from just prior to the second injection through 14 days after the second injection of Camcevi 21 mg (Day 98, week 14) was to be summarized descriptively and a paired t-test or Wilcoxon signed-rank test was to be used under significance level of 0.05. The summary results were to be provided for ITT population and for PP population.

- Effect of Camcevi 21 mg on change of serum prostate-specific antigen (PSA) levels
- Effect of Camcevi 21 mg on change of serum LH levels

The change from baseline for serum PSA levels at scheduled visit and serum LH levels at scheduled visit were to be summarized descriptively and a paired t-test or Wilcoxon signed-rank test was to be used with significance level of 0.05. The summary results were to be provided as for ITT and PP populations.

- The percentage of subject with PSA relapse defined as after achieving the serum PSA level $\leq$ 4 ng/mL post Camcevi 21 mg injection but with an increase in serum PSA of >50% PSA nadir by Day 168 (week 24)
- The percentage of subject achieving normal serum PSA level (< 4 ng/mL) on Day 168 $\pm$ 5 days (week 24)

The subject with PSA relapse was defined as after achieving the serum PSA level $\leq$ 4 ng/mL post Camcevi 21 mg injection but with an increase in serum PSA of >50% PSA nadir by Day 168 (week 24), i.e., subject achieves the serum PSA level $\leq$ 4 ng/mL on Day 28 but with an increase in serum PSA of >50% PSA on Day 84 or Day 168, or subject achieves the serum PSA level $\leq$ 4 ng/mL on Day 84 but with an increase in serum PSA of >50% PSA on Day 168. The incidence of PSA relapse was to be presented as subject count,

percentage, and exact 95% CI for binomial proportion for ITT and PP populations; and the percentage of subject achieves normal serum PSA level was to be presented for ITT and PP populations. Besides, the additional analyses of PSA levels < 4 ng/mL for subjects with elevated PSA at baseline. It is noted that the normal serum PSA level was to be analysed as < 4 ng/mL rather than <4 ng/dL since it is typo on protocol.

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

The percentage of subjects with a serum testosterone ≤ 20 ng/dL on Day 28 ± 1 day (week 4) and on Day 168 ± 5 days (week 24)were to be analysed using a standard large sample normal approximation to a Binomial distribution. The summary results included subject count, percentage and exact 95% CI for binomial proportion was be presented for ITT and PP populations. Based on protocol, the testosterone level was assessed at Week 26 for the first enrolled 30 subjects. The additional analysis of subjects with a serum testosterone concentration suppressed to castrate levels (≤ 50 ng/dL) at Week 26 was to be presented for ITT and PP populations.

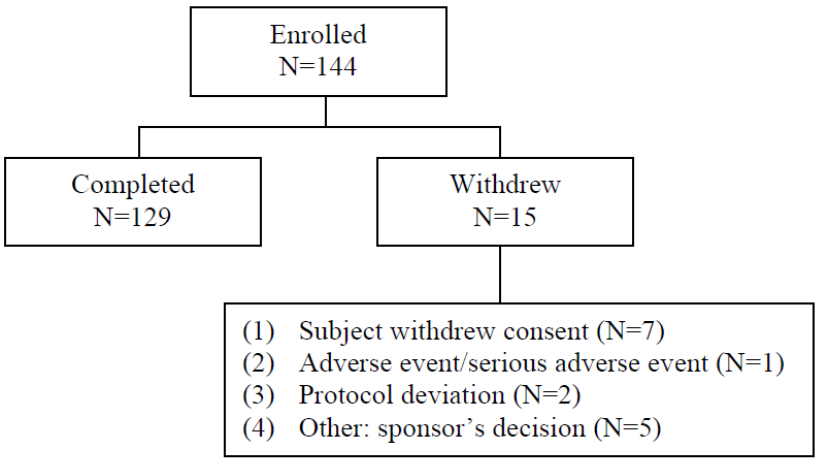
5.3.2.1.4. Results

5.3.2.1.4.1. Participant flow and numbers analysed

A maximum of 133 subjects were anticipated to be enrolled into this study. A total of 144 subjects were enrolled in the study (Figure 10). Of the 144 enrolled subjects, 15 (10.4%) subjects did not complete the study.

Seven subjects terminated early due to consent withdrawal, one subject terminated early due to adverse event/serious adverse event, 2 subjects terminated early due to protocol deviation and 5 subjects) were withdrawn from study by the sponsor's decision because the concern site was found to be incompliant with GCP during monitoring visit. The disposition of patients is presented in Figure 10.

Figure 10: Disposition of patients in study FP01C-17-001



N: number of subject

Several populations were analysed in this study: intention-to-treat (ITT), per protocol (PP), safety, ECG, PK, and ECG/PK populations (Table 23). The ITT and safety populations were defined as any subject who received at least one dose of Camcevi 21 mg. The PP population was defined as subjects who received 2 doses of Camcevi 21 mg without major deviations that affected the assessment of the primary efficacy

endpoint. The ECG population was defined as any subject receiving at least one dose of Camcevi 21 mg and who had an ECG value measured for at least 1 post-dose time point. The PK/ECG population was defined as any subject in the ECG population with post-dose time-matched serum concentrations of leuprorelin or testosterone. The PK population included all subjects who were dosed with Camcevi 21 mg, had at least one evaluable PK parameter, and were not excluded from analysis for protocol deviations or other study-related events that impact the calculation or interpretation of the PK variables.

Table 16: Summary of study population (FP01C-17-001)

Variable/ Status	ITT Population (N=144)
ITT population	
ITT population	144 (100 %)
PP population	
PP population	132 (91.7 %)
Non-PP population	12 (8.33 %)
Safety population	
Safety population	144 (100 %)
ECG population	
ECG population	144 (100 %)
PK/ECG population	
PK/ECG population	144 (100 %)

Twelve subjects were excluded from the PP population because they did not receive the second dose of Camcevi 21 mg.

5.3.2.1.4.2. Deviations from study plan

There was a protocol amendment in November 2017 to the original study protocol from May 2017. In the protocol amendment a new exclusion criteria was added: "(6) Patients who were previously enrolled in the LMIS 50 mg study". Patients previously enrolled in the Camcevi 42 mg study were not excluded in version 1.0 and according to the Applicant, this criterion was added in version 1.1 to avoid potential patient selection bias and for clarification.

In this study, 269 protocol deviations were reported, of which 14 incidences in 13 subjects were reported as major deviations. The other 255 deviations were reported as minor based on the sponsor's internal guidance.

One site was found with significant GCP violations during the study conduct, and at the decision of the Applicant 5 subjects) from this site were withdrawn from the study prior to their intended 2nd doses. Therefore, a total of 144 subjects were finally enrolled in the study FP01C-17-001.

5.3.2.1.4.3. Baseline data

Table 17: Summary of subject demographics and baseline characteristics (ITT population). Source: Module 5.3.5.2 Clinical study report FP01C-17-001

Variable/ Status		Safety/ITT Population (N=144)
Age (years)		
	Mean (SD)	69.8 (7.93)

Variable/ Status		Safety/ITT Population (N=144)
	Median (min, max)	70 (51, 89)
	Hodges-Lehmann estimator	70.0
	95% CI	(68.51, 71.12)
Gender		
	Male	144 (100%)
Race		
	Asian	16 (11.1%)
	Black or African American	1 (0.69%)
	White	127 (88.2%)
Ethnicity		
	Hispanic	4 (2.78%)
	Non - Hispanic	4 (2.78%)
	Subject is not a national of U.S.A.	136 (94.4%)
Diagnosis (days) of prostate carcinoma history*		
	Mean (SD)	842.7 (1348.90)
	Median (min, max)	109 (0, 6649)
	Hodges-Lehmann estimator	429.3
	95% CI	(620.49, 1064.88)
Staging of prostate carcinoma history		
	I	20 (13.9%)
	II	32 (22.2%)
	III	61 (42.4%)
	IV	12 (8.33%)
	Unknown	19 (13.2%)
T (Primary tumor)		
	T1	25 (17.4%)
	T2	41 (28.5%)
	T3	71 (49.3%)
	T4	3 (2.08%)
	Other	2 (1.39%)
	Unknown	2 (1.39%)
N (Regional lymph nodes)		
	N0	97 (67.4%)
	N1	8 (5.56%)
	NX	33 (22.9%)
	Unknown	6 (4.17%)
M (Distant Metastasis)		
	M0	112 (77.8%)
	M1	7 (4.86%)
	Other	1 (0.69%)
	Unknown	24 (16.7%)
ECOG performance status		
	0	135 (93.8%)
	1	9 (6.25%)
* Diagnosis (days) of prostate carcinoma history was calculated as (Date of informed consent - Date of diagnosis).		

Concomitant treatments allowed during the study:

- Bisphosphonates was permitted during the study.
- Denosumab was permitted during the study.

- Supplementation of vitamin D and calcium was allowed during the study if, in the Investigator's opinion, it was needed for the subject's health.
- Plain, over-the-counter, multi-vitamins were permitted during the study.
- Glucocorticosteroids were allowed if being used as a replacement therapy.
- Pain medication was allowed if it was an over-the-counter or prescription medication and prescribed by a physician and as described in the appendix IV of protocol.
- Oral hypoglycemics were allowed for control of Type II diabetes.
- Radiation for pain control was allowed during the study.

Treatment compliance:

Twelve subjects were excluded from the PP population because they did not receive the second dose of Camcevi 21 mg and therefore these subjects did not impact the efficacy analysis. The compliance of receiving 2 doses of Camcevi 21 mg was 91.7%.

5.3.2.1.4.4. Outcomes and estimation

Primary efficacy endpoint:

The primary efficacy endpoint of study FP01C-17-001 was the percentage of subjects with a serum testosterone concentration suppressed to castrate levels (≤ 50 ng/dL) by Day 28 (week 4) following the first injection of Camcevi 21 mg and to determine the proportion of subjects with serum testosterone suppression (< 50 ng/dL) from Day 28 through Day 168 (week 24, EOS).

Table 18: Primary endpoint results for clinical efficacy study FP01C-17-001

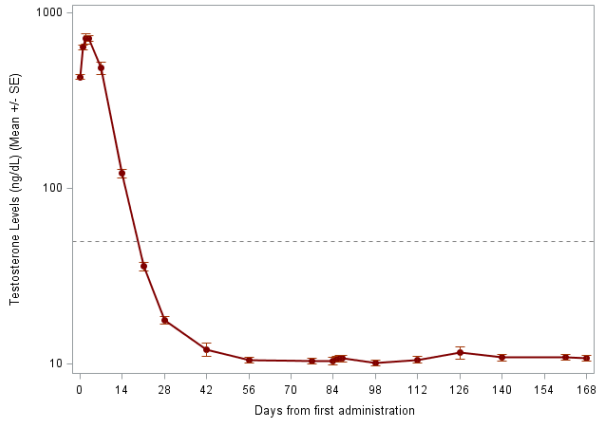
Population	**# Enrolled/ completed**	**Percentage of subjects with serum testosterone ≤ 50 ng/dL (95% CI)**	
		By Day 28	**Day 28–Day 168**
ITT[a]	144/143	98.6 (95.0–99.8)	97.9 (93.5–99.3)
PP[b]	144/132	98.5 (94.6–99.8)	97.7 (93.1–99.3)

[a] Any subject who received at least 1 dose of Camcevi 21 mg
[b] Any subject who received 2 doses of Camcevi 21 mg, met the inclusion/exclusion criteria of the protocol, and had no major protocol violation
CI = confidence interval; ITT = intent-to-treat; PP = per protocol

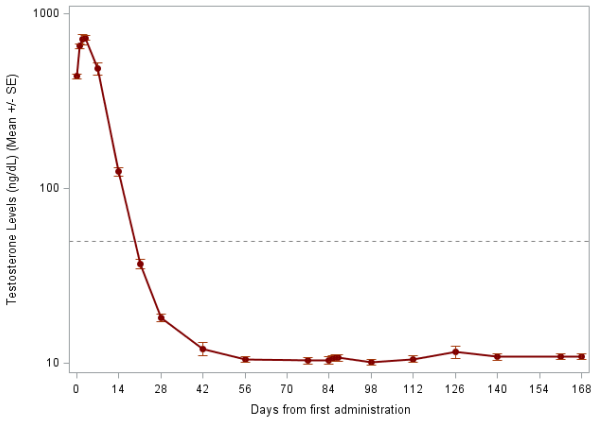
At 7–8 weeks after the first injection, the mean serum testosterone level reached a plateau of approximately 10 ng/dL (Figure 11). Serum testosterone remained at this level until the EOS at week 24 (Day 168).

Figure 11: Mean serum testosterone over time (study FP01C-17-001)

ITT Population:



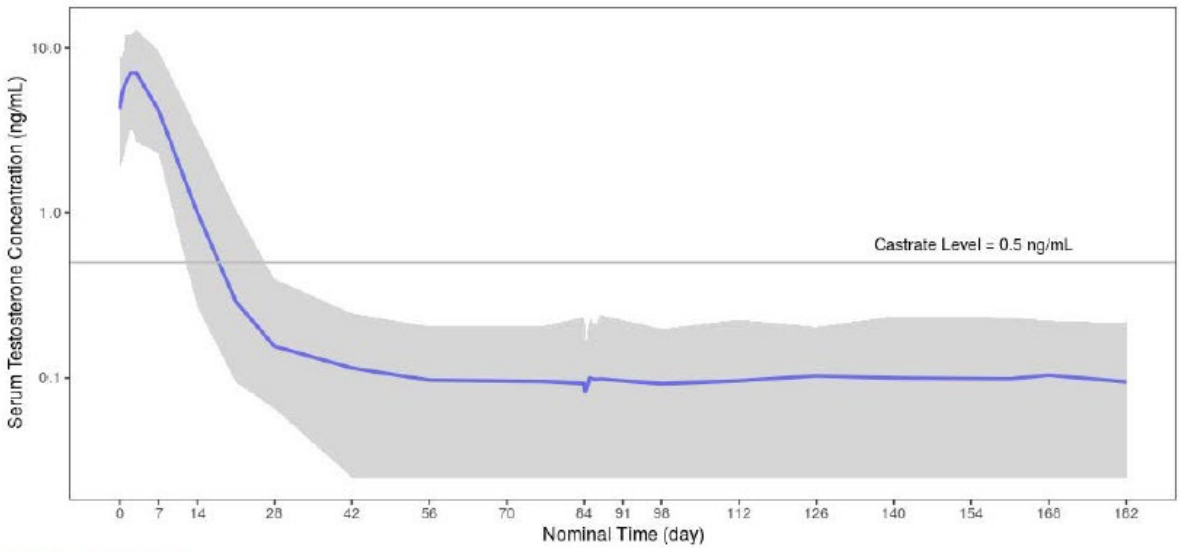
PP Population:



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

Following administration of Camcevi 21 mg, serum testosterone concentration increased until 7 days before decreasing up to Day 28 (Figure 11, Figure 12). Serum testosterone levels remained low (below castrate levels of 0.5 ng/mL) until the end of Period 2. Two subjects did not reach the 0.5 ng/mL serum testosterone target level 4 weeks after SC administration of LMIS in Period 1. Most subjects reached the 0.50 ng/mL serum testosterone target level after 12 weeks (~2000 h).

Figure 12: Median (95% prediction interval) serum testosterone concentration vs. time after a single SC dose of Camcevi 21 mg (Day 0) or multiple SC dose of Camcevi 21 mg (Day 84) [semi-log scale].



Day 84 = 2016 hours

Secondary endpoints:

1. The mean acute-on-chronic (surge) changes in testosterone and LH levels from just prior to the second injection through 14 days after the second injection of Camcevi 21 mg

Testosterone

Table 19 Summary of Acute-on-Chronic Changes in testosterone Levels (ITT Population)

Table 14.2.4: Summary of Acute-on-Chronic Changes in Testosterone Levels (ITT Population)

Variable	Visit	Statistics	ITT Population (N=144)
The mean acute-on-chronic (surge) in testosterone levels (ng/dL)	Day 84 (V13) - 2 Hours Post Dosing	n	3
		Mean (SD)	14.360 (7.7121)
		Median (min, max)	12.6 (7.68, 22.8)
		Hodges-Lehmann estimator	13.920
		95% CI	(-4.7980, 33.5180)
	Day 84 (V13) - 4 Hours Post Dosing	n	12
		Mean (SD)	41.858 (93.4150)
		Median (min, max)	16 (6.9, 338)
		Hodges-Lehmann estimator	16.125
		95% CI	(-17.4947, 101.2114)
	Day 84 (V13) - 8 Hours Post Dosing	n	1
		Mean (SD)	10.20 (-)
		Median (min, max)	10.2 (10.2, 10.2)
		Hodges-Lehmann estimator	10.20
		95% CI	-
	Day 85 (V14)	n	32
		Mean (SD)	12.962 (5.0708)
		Median (min, max)	11.75 (6.6, 27.3)
		Hodges-Lehmann estimator	12.175
		95% CI	(11.1337, 14.7901)
	Day 86 (V15)	n	32
		Mean (SD)	12.967 (5.1462)
		Median (min, max)	13.6 (6.47, 30.3)
		Hodges-Lehmann estimator	12.530
		95% CI	(11.1118, 14.8226)
	Day 87 (V16)	n	30
		Mean (SD)	13.314 (5.7721)
		Median (min, max)	12.65 (6.35, 28)
		Hodges-Lehmann estimator	12.800
		95% CI	(11.1583, 15.4690)
	Day 98 (V17)	n	25
		Mean (SD)	11.503 (3.5907)

Luteinizing hormone

Table 20 Summary of Acute-on-Chronic Changes in LH Levels (ITT Population)

Table 14.2.5: Summary of Acute-on-Chronic Changes in LH Levels (ITT Population)

Variable	Visit	Statistics	ITT Population (N=144)
The mean acute-on-chronic (surge) in LH levels (IU/L)	Day 85 (V14)	n	39
		Mean (SD)	0.25234 (0.564719)
		Median (min, max)	0.114 (0.0636, 3.53)
		Hodges-Lehmann estimator	0.12348
		95% CI	(0.069283, 0.435404)
	Day 86 (V15)	n	38
		Mean (SD)	0.13432 (0.127010)
		Median (min, max)	0.106 (0.0637, 0.814)
		Hodges-Lehmann estimator	0.10975
		95% CI	(0.092574, 0.176068)
	Day 87 (V16)	n	28
		Mean (SD)	0.13421 (0.119585)
		Median (min, max)	0.09365 (0.0698, 0.707)
		Hodges-Lehmann estimator	0.11400
		95% CI	(0.087841, 0.180581)
	Day 98 (V17)	n	12
		Mean (SD)	0.18023 (0.208877)
		Median (min, max)	0.09335 (0.0696, 0.676)
		Hodges-Lehmann estimator	0.09798
		95% CI	(0.047511, 0.312939)
	Percent change at Day 85 (V14)	n	39
		Mean (SD)	145.46 (222.526)
		Median (min, max)	75 (27.2, 1354)
		Hodges-Lehmann estimator	96.25
		95% CI	(73.324, 217.594)
		P-value*	<0.0001
	Percent change at Day 86 (V15)	n	38
		Mean (SD)	101.62 (117.150)
		Median (min, max)	67.85 (27.4, 664)
		Hodges-Lehmann estimator	75.25
		95% CI	(63.112, 140.125)
		P-value*	<0.0001

	Percent change at Day 87 (V16)	n	28
		Mean (SD)	101.82 (78.249)
		Median (min, max)	82.35 (27.1, 350.3)
		Hodges-Lehmann estimator	83.70
		95% CI	(71.480, 132.163)
		P-value*	<0.0001
	Percent change at Day 98 (V17)	n	12
		Mean (SD)	76.95 (81.326)
		Median (min, max)	56.85 (32.1, 330.6)
		Hodges-Lehmann estimator	56.93
		95% CI	(25.278, 128.622)
		P-value*	0.0005

2. The effect of Camcevi 21 mg on change of serum PSA levels; the percentage of subject with PSA relapse by Day 168 (week 24); the percentage of subjects achieving normal PSA level (< 4 ng/mL) on Day 168 (week 24)

The administration of Camcevi 21 mg reduced the serum PSA levels after the first injection, and the effect remained until the end of the study (Table 28 and Figure 13).

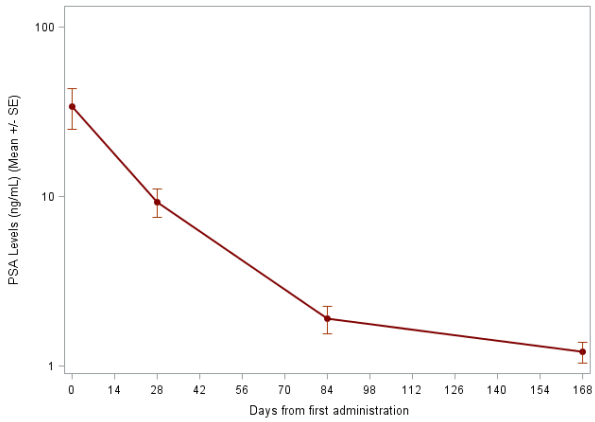
Table 21: Mean serum prostate-specific antigen (PSA) levels over time (study FP01C-17-001)

Serum PSA levels (ng/mL), Mean ± SD			
Baseline	**Day 28**	**Day 84**	**Day 168**
34.204± 109.7483	9.323± 20.9448[#]	1.911± 4.0558[#]	1.212± 2.0106[#]
35.867± 114.0996	9.736± 21.6014[#]	1.911± 4.0558[#]	1.221± 2.0289[#]

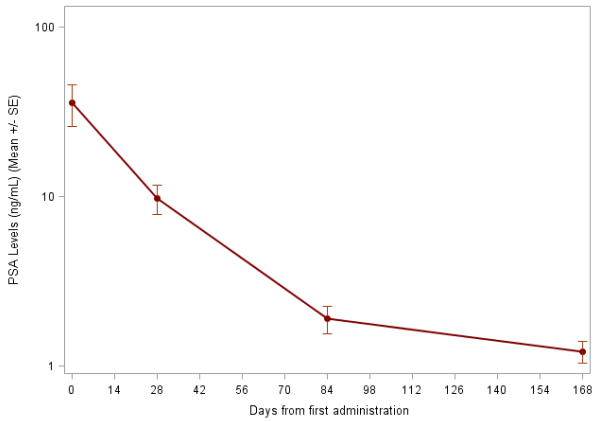
[a] Any subject who received at least 1 dose of Camcevi 21 mg
Any subject who received 2 doses of Camcevi 21 mg, met the inclusion/exclusion criteria of the protocol, and had no major protocol violation
[#]p < 0.001 for change
ITT = intent-to-treat; PP = per protocol; PSA = prostate-specific antigen; SD = standard deviation.

Figure 13: Mean serum prostate-specific antigen (PSA) levels over time (study FP01C-17-001)

ITT Population:



PP Population:



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

PSA relapse was defined as after achieving the serum PSA level ≤ 4 ng/mL post Camcevi 21 mg injection but with an increase in serum PSA of >50% PSA nadir by Day 168 (week 24).

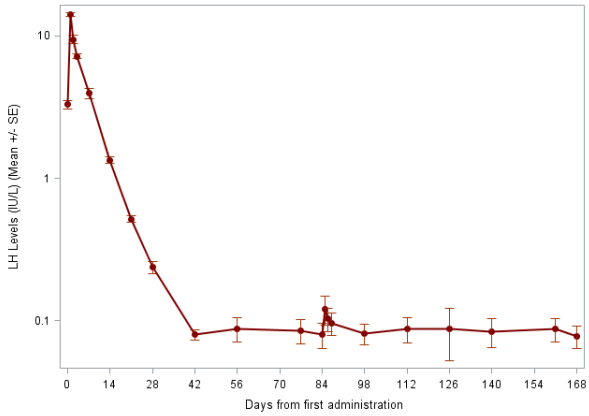
Two subjects in the ITT and PP populations had a PSA relapse. One subject had a PSA level of 1.6 ng/mL on Day 84 (55% increase after achieving PSA nadir) and 2.48 ng/mL on Day 168, and the other subject had a PSA level of 0.23 ng/mL on Day 84 and 0.53 ng/mL on Day 168 (130% increase after achieving PSA nadir).

3. The effect of Camcevi 21 mg on change of serum LH levels

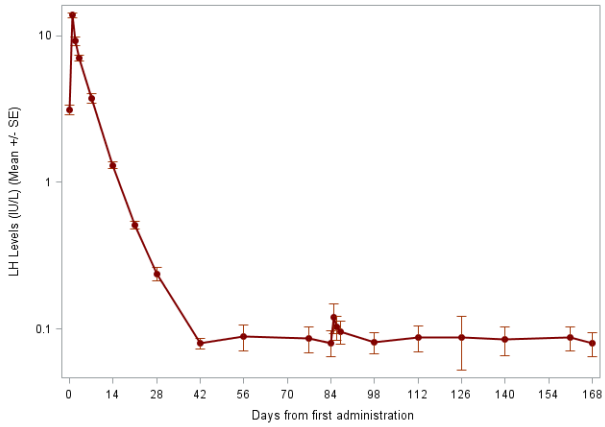
The effect of Camcevi 21 mg on serum LH levels in the ITT and PP study populations is shown in Figure 14.

Figure 14: Mean serum luteinizing hormone (LH) levels over time (study FP01C-17-001)

ITT Population:



PP Population:



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

The administration of Camcevi 21 mg significantly 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 Camcevi 21 mg. Administration of 2 separate doses of Camcevi 21 mg was associated with a significant ($p < 0.001$) reduction of mean serum LH levels by approximately 95% to 97% in the ITT and PP populations, respectively, on Day 168 compared to baseline (Table 29).

Table 22: Summary of LH levels and change from baseline (ITT and PP Populations)

	ITT Population (N=144)			PP Population (N=132)		
Variable / Status	**Summary**	**Change**	**P-value***	**Summary**	**Change**	**P-value***
Day 0 (V2) - Prior Dosing						
n	144			132		
mean (SD)	3.2921 (2.73091)			3.1093 (2.63183)		
median (min, max)	2.545 (0.577, 18.1)			2.475 (0.577, 18.1)		
Hodges-Lehmann estimator	2.7450			2.5650		
95% CI	(2.84225, 3.74194)			(2.65610, 3.56242)		
Day 28 (V9)						
n	143	143	<0.0001	132	132	<0.0001
mean (SD)	0.23677 (0.278775)	-3.04387 (2.666438)		0.23777 (0.288380)	-2.87149 (2.558389)	
median (min, max)	0.179 (0.05, 3.1)	-2.373 (-17.595, 1.2)		0.1785 (0.05, 3.1)	-2.279 (-17.595, 1.2)	
Hodges-Lehmann estimator	0.19800	-2.51250		0.19600	-2.36140	
95% CI	(0.190684, 0.282853)	(-3.484662, -2.603088)		(0.188113, 0.287422)	(-3.312003, -2.430978)	
Day 84 (V13)						
n	132	132	<0.0001	132	132	<0.0001
mean (SD)	0.08047 (0.185865)	-3.02879 (2.634907)		0.08047 (0.185865)	-3.02879 (2.634907)	
median (min, max)	0.05 (0.05, 2.1)	-2.425 (-18.05, 0.2)		0.05 (0.05, 2.1)	-2.425 (-18.05, 0.2)	
Hodges-Lehmann estimator	0.05000	-2.49500		0.05000	-2.49500	
95% CI	(0.048469, 0.112475)	(-3.482473, -2.575098)		(0.048469, 0.112475)	(-3.482473, -2.575098)	
Day 168 (V22/EOS)						
n	140	140	<0.0001	130	130	<0.0001
mean (SD)	0.07818 (0.166157)	-3.14327 (2.724733)		0.07972 (0.172246)	-3.00807 (2.653558)	
median (min, max)	0.05 (0.05, 1.85)	-2.46 (-18.05, -0.05)		0.05 (0.05, 1.85)	-2.39 (-18.05, -0.05)	
Hodges-Lehmann estimator	0.05000	-2.59500		0.05000	-2.45000	
95% CI	(0.050410, 0.105940)	(-3.598576, -2.687960)		(0.049830, 0.109609)	(-3.468532, -2.547599)	

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.

4. The percentage of subjects with enhanced serum testosterone concentration suppression to ≤ 20 ng/dL on Day 28 (week 4) and on Day 168 (week 24)

The efficacy of administration with Camcevi 21 mg in prostate cancer patients was also analyzed by examining the percentage of subjects with the serum testosterone further suppressed to ≤ 20 ng/dL on Day 28 and Day 168 in both ITT and PP populations (Table 30).

Table 23: Subjects with further suppressed serum testosterone level (< 20 ng/dL) (study FP01C-17-001)

	Percentage of subjects with serum testosterone concentration ≤ 20 ng/mL (95% CI)	
	Day 28	**Day 168**
ITT[a]	72% (63.91, 79.21)	96.4% (91.86, 98.83)
PP[b]	71.2% (62.69, 78.76)	96.2% (91.25, 98.74)

[b] Any subject who received at least 1 dose of Camcevi 21 mg
Any subject who received 2 doses of Camcevi 21 mg, met the inclusion/exclusion criteria of the protocol, and had no major protocol violation
CI = confidence interval; ITT = intent-to-treat; PP = per protocol; PSA = prostate-specific antigen

5.3.2.1.4.5. Ancillary analyses

Pre-defined and post-hoc subgroup analyses

The Applicant conducted post-hoc analyses of the data from FP01C-17-001 to re-assess serum testosterone suppression by threshold (< 50 ng/dL, < 20 ng/dL) (Table 31, Table 32). This was done to align with the serum testosterone suppression thresholds proposed in the recent FDA Guidance GnRH Analogues in Prostate Cancer (2022),[22] which recommends a castrate threshold of < 50 ng/dL and the more rigorous threshold of < 20 ng/dL (of note, the protocol-specified primary endpoint was ≤ 50 ng/dL and the protocol-specified secondary endpoint was ≤ 20 ng/dL). These re-assessments followed the same analysis approach originally applied to the primary endpoint of study FP01C-17-001. Re-assessments were carried out and completed in the primary efficacy analysis set, the ITT population (N=144).

Table 24: A comparison of the primary efficacy outcome of study FP01C-17-001 using the protocol specified castrate threshold of ⩽ 50 ng/dL and the castrate threshold of < 50 ng/dL as per FDA Guidance GnRH Analogues in Prostate Cancer (2022)

Percentage of Subjects with Serum Testosterone Suppression (95% CI) (ITT Population)	
Serum Testosterone Level of ≤ 50 ng/dL Protocol-specified	
By Day 28 (Week 4)	Day 28 (Week 4) through Day 168 (Week 24)
98.6% (95.04, 99.83)	**97.9% (93.5, 99.3)**
Serum Testosterone Level of < 50 ng/dL as per FDA Guidance	
By Day 28 (Week 4)	Day 28 (Week 4) through Day 168 (Week 24)
98.6% (95.04, 99.83)	**97.9% (93.5, 99.3)**

CI = confidence interval

[24] Smith MR, Lee H, Fallon MA, Nathan DM. Adipocytokines, obesity, and insulin resistance during combined androgen blockade for prostate cancer. Urology. 2008 Feb;71(2):318-22. doi: 10.1016/j.urology.2007.08.035. PMID: 18308111; PMCID: PMC2614378.

Table 25: The percentage of subjects with the more stringent serum testosterone suppression to levels < 20 ng/dL as per FDA Guidance GnRH Analogues in Prostate Cancer (2022) following subcutaneous administration of Camcevi 21 mg in the ITT analysis set (study FP01C-17-001)

Analysis Set	Percentage of Subjects with Serum Testosterone Suppression < 20 ng/dL (95% CI)	
	By Day 28 (Week 4) (n=143)[a]	Day 28 (Week 4) through Day 168 (Week 24) (n=143)[a]
ITT (N=144)	71.3% (63.18, 78.58)	63.0% (50.7, 73.0)

[a] One subject withdrew consent from the study and did not have testosterone level at Day 28; the subject's last testosterone level was 11.9 ng/dL at Day 21. Therefore, the subject number for analysis was 143.
CI = confidence interval; ITT = intent-to-treat

Pre-defined and post-hoc sensitivity analyses

Pre-defined sensitivity analysis:

Sensitivity analyses for the primary efficacy endpoint were performed in both the ITT and PP analysis set, and revealed that the percentage of subjects with testosterone suppression (≤ 50 ng/dL) from week 4 through week 24 was 97.8% (132 out of total 135 subjects; 95% CI: 93.2-99.3) and 97.7% (128 out of 131 subjects; 95% CI: 93.1-99.3), respectively. All lower 95% CI bounds for the suppression rate were greater than 90%.

Post-hoc sensitivity analysis:

The Applicant also conducted post-hoc sensitivity analyses of the data from the study FP01C-17-001 (ITT population) on the also re-assessed primary efficacy endpoint, serum testosterone suppression < 50 ng/dL, as per FDA Guidance GnRH Analogues in Prostate Cancer (2022).[23] These sensitivity analyses comprised the following:

- Sensitivity analysis of missing values not censored as per the protocol of Study FP01C- 17-001 but considered treatment failures, regardless of serum testosterone levels before and after missing time points
- Sensitivity analysis handling dropouts and subjects with two or more consecutive missing values as treatment failures, regardless of serum testosterone levels before and after missing time points
- Sensitivity analyses considering subjects who received concomitant medications and herbal supplements that could possibly affect serum testosterone levels, either censored / considered treatment failures or completely excluded from analysis.

Camcevi 21 mg suppressed serum testosterone concentrations to < 50 ng/dL even if missing values previously handled as censored as specified in the protocol of Study FP01C-17-001 were alternatively handled as therapeutic failures. A further sensitivity analysis taking the approach of handling dropouts and subjects with consecutive missing values as treatment failures, irrespective of serum testosterone levels before and after missing time points, showed that Camcevi 21 mg effectively suppressed serum testosterone concentrations to < 50 ng/dL. Two additional sensitivity analyses considering co-medications potentially interfering with serum testosterone levels (respective subjects either considered treatment failures / censored or excluded from analysis) and the potential impact on the primary efficacy endpoint (serum testosterone suppression < 50 ng/dL) showed that Camcevi 21 mg effectively suppressing serum testosterone below the castrate threshold.

Subgroup analyses

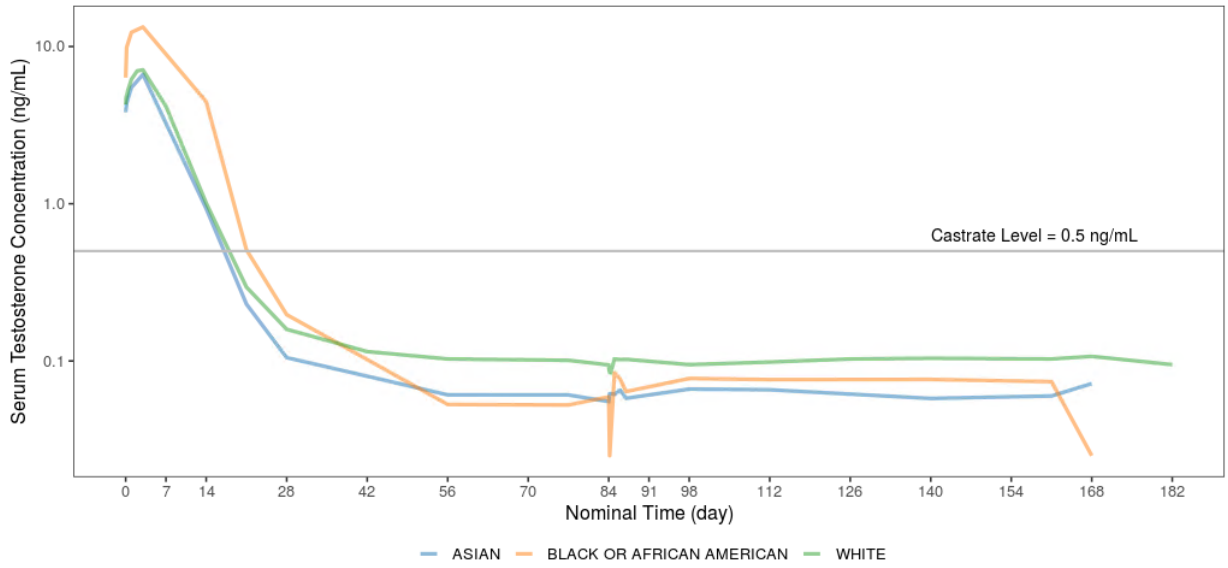
[24] Smith MR, Lee H, Fallon MA, Nathan DM. Adipocytokines, obesity, and insulin resistance during combined androgen blockade for prostate cancer. Urology. 2008 Feb;71(2):318-22. doi: 10.1016/j.urology.2007.08.035. PMID: 18308111; PMCID: PMC2614378.

Subgroup analyses were conducted for the 144 subjects in the PK population of FP01C-17-001. Analyses included race, age, and body weight.

Race

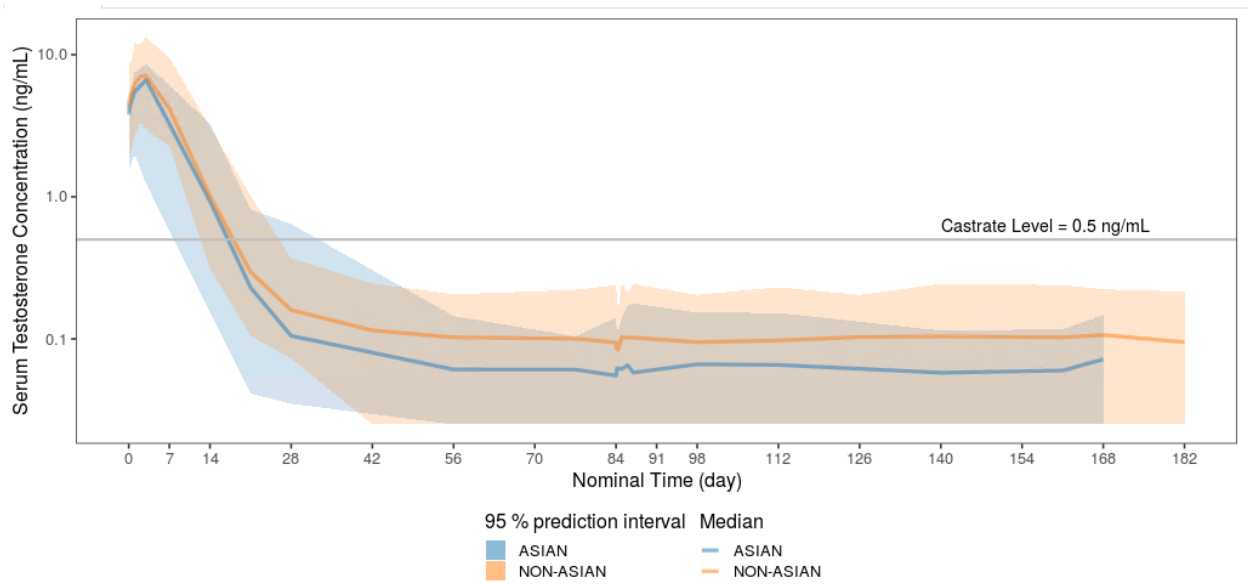
Median serum testosterone concentration time profiles were similar among races with Day 28 levels < 0.5 ng/mL (Figure 15). Median serum testosterone concentration-time profiles were lower in Asian subjects compared to non-Asian subjects (Figure 16). However, both groups' median profiles reached the 0.5 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 168).

Figure 15: Race differences in serum testosterone levels (study FP01C-17-001)



Median serum testosterone concentration vs time after a single subcutaneous dose of Camcevi 21 mg (Day 0) or multiple doses (Day 84) by race (semi-log scale)

Figure 16: Asian vs non-Asian serum testosterone levels (study FP01C-17-001)

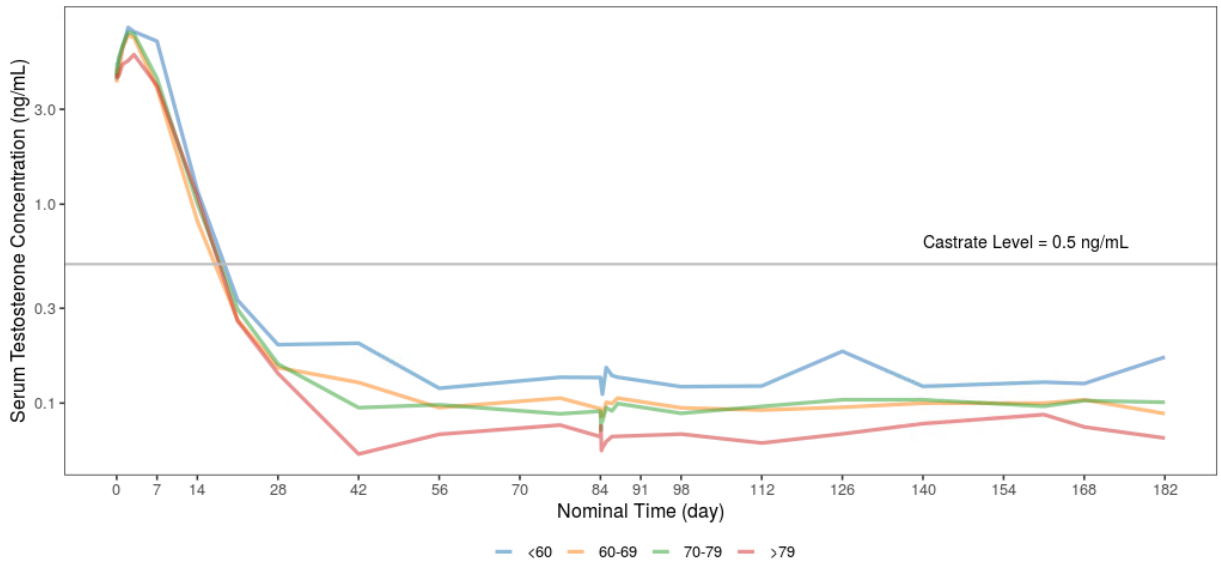


Median (95% prediction interval) serum testosterone concentration vs time after a single subcutaneous dose of Camcevi 21 mg (Day 0) or multiple doses (Day 84) in Asian and non-Asian subjects (semi-log scale)

Age

A comparison of testosterone levels by age categories (<60, 60-69, 70-79, or >79 years old) are presented in Figure 17.

Figure 17: Age differences in serum testosterone levels (study FP01C-17-001)



Median serum testosterone concentration vs time after a single subcutaneous dose of Camcevi 21 mg (Day 0) or multiple doses (Day 84) by subjects' age categories (semi-log scale).

Across age categories, peak concentration of serum leuprorelin was increased 1.8-fold in subjects aged > 79 years compared to subjects aged < 60 years. Total serum leuprorelin exposure was also increased with age, as a 2-fold increase was observed at 3 months following Camcevi 21 mg administration in subjects aged > 79 years compared to subjects < 60 years. The relationship between serum leuprorelin PK parameters and age was statistically significant ($p \leq 0.001$).). (See Clinical Pharmacology)

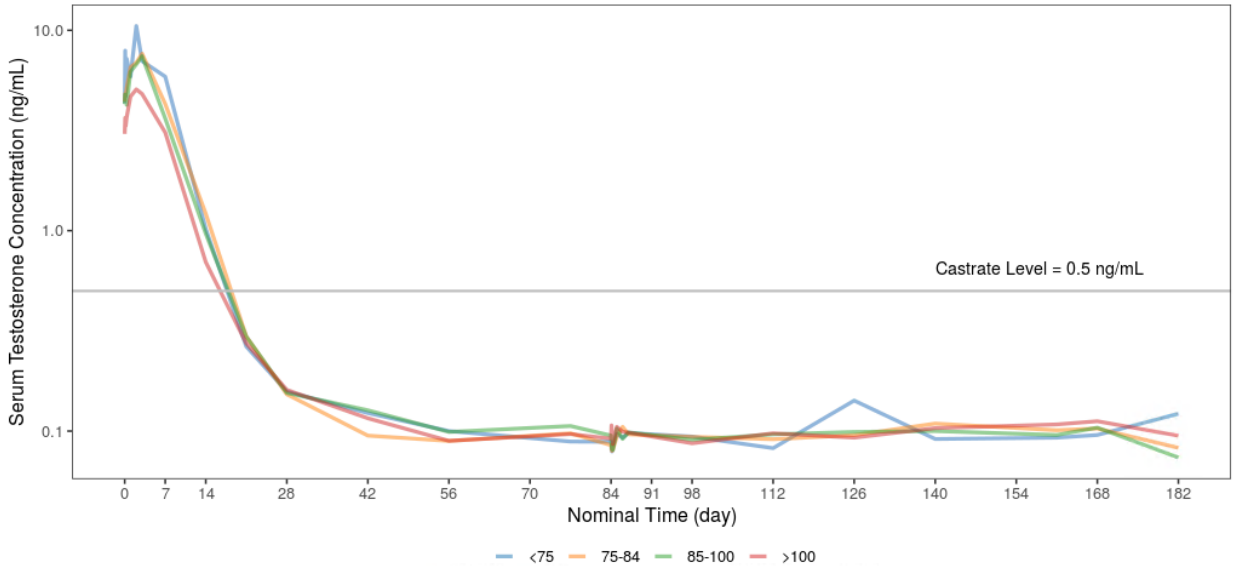
Body weight

A comparison of median serum testosterone levels by body weight categories (<75, 75-84, 85–100, or >100 kg) are provided in Figure 18. *C*oncentration time profiles were comparable among body weight categories.

In the published literature, one published study analysed testosterone suppression by subgroups based on body mass index (Smith 2007).[24] During treatment with leuprorelin 22.5 mg 3-month depot, obese men had significantly higher total testosterone levels than men with normal BMI, despite lower baseline serum testosterone levels. Specifically, mean total testosterone levels during treatment were 1.8-fold higher in obese men, though the mean values remained within the castrate range (Week 24: 11 + 1 ng/dL versus 20 + 3 ng/dL; Week 48: 10 + 1 ng/dL versus 18 + 3 ng/dL). Similarly, men with body fat mass >25% had significantly higher total testosterone levels during treatment with leuprorelin depot than men with lower percentage body fat.

[24] Smith MR, Lee H, Fallon MA, Nathan DM. Adipocytokines, obesity, and insulin resistance during combined androgen blockade for prostate cancer. Urology. 2008 Feb;71(2):318-22. doi: 10.1016/j.urology.2007.08.035. PMID: 18308111; PMCID: PMC2614378.

Figure 18: Body weight differences in serum testosterone levels (study FP01C-17-001)



Median serum testosterone concentration vs time after a single subcutaneous dose of Camcevi 21 mg (Day 0) or multiple dose (Day 84) by body weight categories (kg) [semi-log scale].

5.3.3. Clinical studies in special populations

Table 33 and Table 34 describe the special populations in the clinical study FP01C-17-001.

Table 26: Clinical studies in special populations in the clinical study FP01C-17-001

	Controlled Trials	Non-controlled trials
Renal impairment* patients (Subjects number /total number)	NA	20/144
Hepatic impairment** patients (Subjects number /total number)	NA	6/144
Paediatric patients <18 years (Subjects number /total number)	NA	NA
Older patients; Age 65-74 (Subjects number /total number)	NA	63/144
Age 75-84 (Subjects number /total number)	NA	40/144
Age 85+ (Subjects number /total number)	NA	4/144
Other (Subjects number /total number)	NA	NA

* The renal impaired medical histories were derived from the following preferred terms: Chronic kidney disease, Diabetic nephropathy, Dysuria, Haematuria, Nephrolithiasis, Nephrosclerosis, Neurogenic bladder, Nocturia, Renal cyst, Renal impairment and Urinary retention.
** The hepatically impaired medical histories were derived from the following preferred terms: Alcoholic liver disease, Cholelithiasis, Hepatic cyst, Hepatic steatosis, Hyperbilirubinaemia, and Liver disorder.
NA = not applicable

Table 27: Summary of eGRF at baseline (ITT population). Renal impairment is defined as having Chronic Kidney Disease (CKD) stages

	Variable/ Status	ITT Population (N=144)
Renal Function		
	n	144
	Normal	44 (30.56 %)
	Mild impairment	93 (64.58 %)
	Moderate impairment	7 (4.86 %)
	Severe impairment	0 (0 %)

Elderly population

The main study FP01C-17-001 protocol enrolled male patients who were ≥ 18 years old. The age distribution is presented in Table 33.

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 × ULN
- AST (SGOT) ≤ 2.5 × ULN
- ALT (SGPT) ≤ 2.5 × ULN
- Serum creatinine ≤ 1.5 mg/dL

All subjects with moderate renal impairment maintained castrate-level testosterone suppression throughout the 168-day period. In the mild renal impairment group, in 3 subjects (3.3%) testosterone suppression was not maintained at a mean time of 55.8 days, resulting in a 96.7% maintenance rate at Day 168. Data not shown.

Regarding hepatic impairment, no Child-Pugh information was collected. Six patients had hepatically impaired medical histories. One patient had abnormal liver enzymes at Day 28. Data not shown.

5.3.4. Supportive studies

Efficacy results from the published literature on other leuprorelin depot products

A literature search identified a total of 15 relevant clinical studies, including the main clinical studies supporting Lupron Depot 22.5 mg (Sharifi et al. 1996) and Eligard 22.5 mg (Chu et al., 2002) (Table 35). A literature search was conducted in PubMed on 25-Aug-2024 using the search terms leuprolide depot, 3-month (and related synonyms), and prostate cancer, to identify relevant published clinical studies related to the proposed indication for 3-monthly administered 22.5 mg leuprolide products.

A transient increase in serum testosterone levels with initial leuprorelin dosing, followed by rapid reductions of serum testosterone to castrate levels (≤ 50 ng/dL) within approximately 4 weeks that plateaued at low levels throughout, was reported in these published studies. With 6 months of leuprorelin ADT, suppression in serum testosterone at castrate levels (≤ 50 ng/dL) was reported in at least 94% of patients (Braeckman

and Michielsen, 2014; Chu et al., 2002; Schulman et al., 2016; Sarifi et al., 1996; Shore et al., 2019). In studies reporting on the more rigorous castrate threshold of 20 ng/dL, 51.4% to 94.0% of patients had serum testosterone suppressed to either levels < or ≤ this threshold for the periods observed (up to 12 months) (Chu et al., 2002; Malek et al., 2022; Oefelein and Cornum, 2000; Shore et al., 2019; Tombal, 2017) A transition study on initial ADT with the GnRH receptor agonist degarelix followed by a switch-over to leuprorelin also confirmed effective serum testosterone suppression with leuprorelin, maintaining effective ADT subsequent to degarelix (Zuckerman et al., 2014). Effective disease control by respective reduction in serum PSA levels with leuprorelin 3-month depot forms was also reported throughout.

Table 28: Efficacy data for prostate cancer patients treated with leuprorelin acetate 22.5 mg, 3-month depot formulations from published literature studies

Reference	Treated Population	Dose of Leuprorelin[a]	Treatment Duration	Efficacy Findings
Malek et al. 2022	n = 106 median age 71.5 years (range 50-90)	Eligard 22.5 mg, SC injection, once every 3 months	15 months	Of the original 106 patients, 105 were included in the full analysis set (FAS) and 65 were included in the per-protocol set (PPS). At 12 months, 51.4% of patients had testosterone levels <20 ng/dL in the FAS, which increased to 61.9% after 18 months of treatment. In the PPS, 80.0% of patients had testosterone levels <20 ng/dL after 12 months, which remained constant at 18 months. In both populations, <2% of patients had testosterone levels >50 ng/mL at 12-18 months. At 18 months (3 months after the last dose), the percentage of patients with testosterone levels <20, 20-50, and >50 ng/dL was 61.9%, 16.2%, and 1.9%, respectively; 20% had missing testosterone measurements. PSA reduction of ≥90% from baseline at 12 and 18 months occurred in 81.2% and 68.5% of patients, respectively, in the FAS and in 81.5% and 74.6%, respectively, in the PPS.
Shore et al. 2019	n = 163 mean age 71.0 years (range 47-91)	Luprorelin acetate 22.5 mg, IM injection, once every 3 months (Day 0 and Day 84)	6 months (168 days)	Of the original 163 patients, 151 completed the 6-month study. Castrate levels of testosterone (≤ 50 ng/dL) were achieved by 99.4% of patients by day 28 and maintained from days 28-168 in 96.8% (95% CI, 92.5, 98.7) of patients. On day 28, 78.9% of patients achieved a more stringent criterion of testosterone ≤20 ng/dL which was maintained from day 28 onward. On day 168, 98.7% had castrate testosterone levels ≤ 50 ng/dL, and 94.0% had testosterone levels ≤20 ng/dL. After the first administration of leuprorelin acetate 22.5-mg depot, there was an initial increase above baseline levels in mean serum LH concentrations at 1 and 4 h after dosing followed by a decrease below baseline level on day 14. From day 28 to study end, mean serum LH concentrations were below the LLOQ at all time points. At study end, mean serum PSA was reduced by 94.7% from baseline. At baseline, 66.7% had serum PSA concentrations that were ≥4 ng/mL. At 12 and 24 weeks of treatment, 87.6% and

Reference	Treated Population	Dose of Leuprorelin[a]	Treatment Duration	Efficacy Findings
				89.1% of patients with elevated PSA levels at baseline achieved a PSA <4 ng/mL, respectively.
Ohlmann and Gross-Langenhoff 2018	n = 633 median age 75.0 years (range 70.0 to 79.0)	Eligard 22.5 mg, SC injection, once every 3 months	12 months	Of the original 633 patients, 553 had evaluable data at all study visits. Serum PSA was reduced 96% from baseline (median 13.8 ng/mL) to 12 months (median 0.5 ng/mL).
Schulman et al. 2016 (main study), Tombal 2017 (post-hoc analysis)	n = 932 (induction phase), n = 701 (randomized phase) Age not specified	Eligard 22.5 mg, SC injection, once every 3 months	3 months (induction phase), 42 months (randomized phase)	**Induction Phase:** Patients received SC leuprorelin acetate 22.5 mg once every 3 months, for a total of 2 injections in 6 months Median testosterone levels for all patients decreased from 397 ng/dl to 11.0 ng/dl at month 3 (97.2%), with a further small decline at month 6. Median PSA levels decreased from 8.6 ng/ml to 0.20 ng/ml at month 3 and remained at this level at month 6. **Randomized Phase:** Patients underwent either continuous androgen deprivation (CAD, Eligard 22.5 mg every 3 months) or intermittent androgen deprivation (IAD, Eligard 22.5 mg only if serum PSA increased to $\geq$ 2.5 ng/mL) between Month 6 and Month 42 Most CAD patients maintained castrate levels of testosterone throughout treatment (values remained between 9.0 and 12.9 ng/dl), with breakthrough events occurring in 22 patients (6.3%). For the IAD group, who received fewer injections of Eligard (median 12 vs 3 injections), mean testosterone levels increased after randomization (range: 61.0−268.0 ng/dl), and at 36 month mean testosterone was 174.3 ng/dl. PSA remained low in both groups over time, and there was no difference in mean PSA levels over time. **Post-hoc Analysis (CAD group)** (Tombal 2017)**:** In the first 12 months of therapy after randomization, a total of 90.1%, 83.5%, and 74.5% of patients receiving CAD achieved minimum (>50 ng/dL), median (>20 to $\leq$50 ng/dL), and maximum ($\leq$20 ng/dL) suppression of testosterone. Cause-specific survival and time to PSA progression did not differ according to testosterone levels in the first year of therapy.
Zuckerman et al., 2014	n = 48 mean age 73 ± 8 years (range 59-86)	Leuprorelin acetate 22.5 mg, SC injection, single dose	3 months	Of the original 48 patients, 45 were included in the final analysis. Subjects received 3 monthly depot injections of degarelix, a GnRH receptor agonist, followed by one 3-month depot injection of leuprorelin, then were followed for 3 months.

Reference	Treated Population	Dose of Leuprorelin[a]	Treatment Duration	Efficacy Findings
				On transition from degarelix to leuprorelin (day 90), there was a rise in testosterone from the nadir of 16.5 ng/dL to a peak of 25.8 ng/dL (P =.0005), occurring at day 93. Four patients (8.9%) experienced a testosterone surge with a mean peak serum testosterone of 80.7 ng/dL; all 4 returned to castrate levels (≤ 50 ng/dL) within 7 days, and all remained asymptomatic throughout the testosterone fluctuation. On transition from degarelix to leuprorelin (day 90), PSA was reduced from 1.6 ± 3.7 ng/mL to 0.92 ± 1.7 ng/mL (P = 0.001).
Braeckman and Michielsen 2014	n = 224 median age 76.4 years (IQR 70.1-81.1)	Leuprorelin acetate 22.5 mg (Depo-Eligard), SC injection, once every 3 months	At least 3 months (median follow-up time of 132 days)	Of the original 247 patients, 224 were included in the ITT analysis. Median testosterone levels declined from 360 ng/dl at baseline to 20 ng/dl (a 94% reduction). Median serum PSA levels declined from 12.0 ng/ml at baseline to 0.60 ng/ml (a 95% reduction).
Smith 2007	n = 49 mean age 66 ± 1 year	Lupron Depot 22.5 mg, IM, once every 12 weeks	48 weeks	**Note:** Some study patients overlap with the study reported below (Smith et al., 2001). Mean serum testosterone concentrations decreased from 372 ± 18 ng/dL at baseline to 13 ± 1 ng/dL at week 48 (P < 0.001). Total serum testosterone decreased to <50 ng/dL in all subjects.
Smith et al., 2001 (main study), Smith et al., 2002 (BMI subgroup)	n = 47 (main study), n = 40 (subgroup) mean age 66 ± 2 years	Leuprorelin acetate 22.5 mg (Lupron Depot), IM injection, once every 12 weeks (n=22) OR Lupron depot as above + pamidronate (60 mg IV over 2 hours every 12 weeks) (n=21)	48 weeks	Of the original 47 patients, 41 completed the study and 32 were evaluable for the subgroup analysis. Serum testosterone concentrations decreased by 96.3% ± 0.4% (P < 0.001) from baseline to Week 48 Serum PSA concentrations decreased significantly by 88.4% ± 2.8% (P < 0.001) from baseline to Week 48, and all men had PSA responses.
Chu et al., 2002 (main study), Shore et al., 2017 (post-hoc analysis)	n = 117 mean age 73.1 years (range 46-85)	LA-2250 (Eligard 22.5 mg), SC injection, once every 3 months (Day 0 and Day 84)	6 months (168 days)	Of the original 117 patients, 111 completed the study. By Day 28, 98% of patients had serum testosterone ≤ 50 ng/dL and 84% had achieved ≤ 20 ng/dL. At study completion, all patients had serum testosterone ≤ 50 ng/dL, and 94% had ≤ 20 ng/dL. The mean (SE) serum testosterone concentration at the end of the study was 10.1 (0.7) ng/dL, and 90% of patients achieved serum testosterone ≤20 ng/dL within 6 weeks (Shore 2017). From baseline to month 6, mean LH decreased from 9.2 ± 1.1 to 0.08 ± 0.01 mIU/ml.

Reference	Treated Population	Dose of Leuprorelin[a]	Treatment Duration	Efficacy Findings
				From baseline to month 6, mean PSA decreased 98% from 86.4 ± 48.8 ng/mL to 1.7 ± 0.5 ng/mL.
Sharifi et al., 2002	n = 33 mean age 75.1 years	Leuprorelin acetate 22.5 mg (Lupron depot 22.5 mg), IM injection, once every 3 months (13 weeks)	52 weeks (4 injections total)	Of the original 33 patients, 28 completed the study. Mean serum testosterone decreased rapidly from 453.1 ng/dL at baseline to 26.3 ng/dL by Week 3 and to 6.8 ng/dL at the end of the study (a 98.5% reduction). Median time to suppression of serum testosterone (≤ 50 ng/dL) was 21 days (range 15 to 29 days). A minor "escape" from suppression occurred in 1 (3.3%) patient at Week 6 only. Subsequent injections did not produce acute increases in testosterone.
Oefelein and Cornum 2000	n = 38 mean age 70.7 years (95% CI 68-73)	Leuprorelin acetate 22.5 mg (Lupron depot 22.5 mg), IM injection, once every 12 weeks	Not specified (measurements taken every 28 days beginning 90 days after last dose)	**Note**: Of the 38 patients studied, 37 received Lupron depot 22.5 mg while 1 received goserelin acetate 10.8 mg (3M depot). Results below are limited to patients who received Lupron. Castrate levels of testosterone (< 50 ng/dL) were reported in all but 2 (94.6%) patients. Further suppression of testosterone (≤ 20 ng/dL) was achieved in all but 4 (89.2%) patients. Patients who did not reach castration levels of testosterone all had nadir PSA of < 4 ng/mL.
Sharifi et al., 1996	n = 94 (across 2 studies) mean age 70 years (range 53-86)	Leuprorelin acetate 22.5 mg (Lupron depot 22.5 mg), IM injection, once every 12 weeks	24 weeks	Of the original 94 patients, 92 were included in the efficacy analysis. Castrate levels of testosterone (≤ 50 ng/dL) occurred in all assessable patients at some time during the study. In 87 patients (95%), castrate testosterone levels occurred within 30 days after the initial depot injection. Of the remaining 5 patients, 3 achieved castrate testosterone levels by week 8, and onset was achieved at weeks 15 and 28, respectively, in the remaining 2 patients. Two patients experienced a transient escape of serum testosterone; these escapes were not associated with any clinical sequelae. There was an initial increase in LH to above the baseline level on day 4, followed by a decline to below the baseline level by week 2, and a further decline to the lower end of the normal range (3 to 10 mIU/mL) by week 4, where it remained throughout the 24-week treatment period. PSA normalized during the initial 24-week treatment period in 45 (63%) of the 72 patients with elevated baseline values and at least one treatment value. At week 24, PSA decreased by at least 50% in 96% of the patients with elevated baseline values.

IM = intramuscular; LH = luteinizing hormone; LLOQ = lower limit of quantitation; LTFU, long-term follow-up; PSA = prostate specific antigen; SC = subcutaneous; SE, standard error

[C]Concomitant or add-on therapies, such as bicalutamide, are not included for brevity.

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

Not applicable.

5.3.6. Observational data, Data from registries

No Real-World Data (RWD) was provided by the Applicant.

5.3.7. Patient experience data (PED)

No patient experience data concerning efficacy was provided.

5.3.8. Healthcare professional engagement

No information on healthcare professional engagement was provided.

5.3.9. Overall discussion and conclusions on clinical efficacy

5.3.9.1. Discussion

Study design, patient population and conduct of clinical studies

The pivotal efficacy study (FP01C-17-001), conducted with Camcevi 21 mg, was a single clinical phase 3, uncontrolled, multicentre, open-label, single-arm, 6-month, safety and PD/efficacy study performed in 144 male patients with prostate carcinoma in need for androgen deprivation therapy (adult male patients with histologically confirmed prostate carcinoma, baseline morning serum testosterone level > 150 ng/dL, ECOG performance status ≤ 2, with a life expectancy of at least 18 months).

Patients were scheduled to receive two doses of Camcevi 21 mg, 3 months apart. To evaluate the sustained castration testosterone level after two doses of Camcevi 21 mg injections, the first 30 subjects had extended sampling time points to establish the full PK/PD profile of serum leuprolide.

Information provided by the Applicant confirmed that the same clinical study (Study AGL-9909) was the pivotal registration study of Eligard 22.5 mg to support both the application in the US and the line extension MAA in Europe through a mutual recognition procedure, in which Germany (BfArM) was the RMS. Based on the above, the bridging study to Eligard 22.5 mg is acceptable.

No European scientific advice was requested.

Amendments

The study protocol was amended once. The original protocol was dated 27-May-2017 and the latest version 1.1 was dated 23-Nov-2017. The amendment concerned, besides administrative changes and typos, a new exclusion criteria "(6) Patients who were previously enrolled in the LMIS 50 mg study". Patients previously enrolled in the LMIS 50 mg study were not excluded in version 1.0 and this criterion was added in version 1.1 to avoid potential patient selection bias and for clarification. The study was performed in accordance with its study protocol.

Study objectives

Clinical study design and endpoints can be considered acceptable for documenting the biological activity and safety of the proposed formulation of leuprorelin. Also, a comparative study could have been performed, and prostate cancer being one of the most prevalent malignancies, this option would have been feasible. However, for demonstration of a bridge between Camcevi 21 mg and EU-Eligard 22.5 mg, the performance of a single arm study can also be accepted, as the bridge to the reference product data has been shown.

Participant flow and numbers analysed

Several populations were analysed: ITT, PP, safety, ECG, PK, and ECG/PK populations. A maximum of 133 subjects were anticipated to be enrolled into this study. A total of 144 subjects were enrolled in the study. The duration of recruitment was approximately 10 months, and total 186 patients were screened. Of the 144 patients enrolled, 129 completed the study treatment. In total, 15 patients discontinued study. In general, the numbers or discontinued patients are considered acceptable, and the reasons for discontinuations typical for the study population. The CHMP considers the data acceptable.

Baseline characteristics

There were 93.8% (135/144) subjects with Grade 0 and 6.25% (9/144) subjects with Grade 1 ECOG performance status. Thus, the majority of the patients were in good fit with relatively little symptoms not reflecting the patient population with advanced prostate cancer seen in clinical practise. Of note, the study protocol would have allowed ECOG performance status ≤ 2. The study population may not fully represent the real-world population with advanced prostate cancer, however, this issue is not expected to hamper efficacy assessment.

8.33% (12/144) of patients had prostate carcinoma stage IV, 42.4% (61/144) had stage ≥ III, 22.2% (32/144) stage II and 13.9% (20/144) had stage I. Staging was unknown for 13.2% (19/144) patients. The majority, 50.7% (73/144) of the patients had prostate carcinoma stage $\geq$ III commonly causing minor or major disease-related symptoms reflecting a discrepancy between the study population and the real-world situation. It can be concluded that the patient population was highly selected, but this is not expected to have major impact on the primary efficacy endpoint, i.e., testosterone suppression.

Therapies that were allowed during the study per protocol were acceptable as part of good clinical management and they are not considered to affect the efficacy results.

Deviations from study plan

All together 269 protocol deviations were reported, of which 14 incidences in 13 patients were reported as major deviations.

Majority of deviations were considered procedural deviations and related to Good Clinical Practice compliance. These deviations are not considered to affect the efficacy or safety assessment of Camcevi 21 mg.

The 255 minor deviations comprised missing information in reporting of, e.g., bone pain, vital signs, QoL, and ECG. Also, haematology samples were clotted or study visits were conducted on incorrect days or leuproline mesylate and testosterone levels were not sampled within the specified 4-hour post-dosing window. These minor protocol deviations highlight various procedural lapses and non-compliances with the study protocol, often due to logistical issues, patient non-compliance, or administrative oversights.

Efficacy results

Primary endpoint of testosterone levels

The percentage of patients with a serum testosterone of ≤ 50 ng/dL (castrate level) by Day 28 was 98.6% (141 out of total 143 subjects with data on Day 28) in the ITT population. The percentage of patients with testosterone suppression from Day 28 through Day 168 was 97.9% (140 out of 143) in the ITT population and was 97.7% (129 out of 132) in the PP population. There were two subjects who did not reach the castrated level of serum testosterone by Day 28. However, both subjects' serum testosterone levels were < 50 ng/dL (17.7 ng/dL and 35 ng/dL, respectively) by Visit 11 (Day 56) and their testosterone levels remained at castrated level until the EOS. The Applicant clarified that the non-castrate level of one subject was attributed to delayed LH suppression, likely related to chronic kidney disease-associated PK variability, whereas for the other subject it was associated with obesity-related slow drug release (BMI 34). The CHMP considers the data acceptable.

Secondary endpoint 1: The mean acute-on-chronic (surge) changes in testosterone and LH levels from just prior to the second injection through 14 days after the second injection of Camcevi 21 mg

Transient increases in testosterone and LH were observed following the second Camcevi 21 mg injection, consistent with the well-known acute-on-chronic (flare) phenomenon associated with LH-RH analogues. The highest mean testosterone increase occurred shortly after dosing (4 hours post dosing on Day 84 in 12 of 144 subjects), but mean serum testosterone levels remained below the castrate threshold. LH levels showed transient post-dose increases but remained suppressed below baseline and within the normal range until end of study. This phenomenon has been previously discussed in the MAA for Camcevi 42 mg and is recognised in international guidelines[25,26]; therefore, it is not pursued further.

Secondary endpoint 2: The effect of Camcevi 21 mg on change of serum PSA levels; the percentage of subject with PSA relapse by Day 168 (week 24); the percentage of subjects achieving normal PSA level (< 4 ng/mL) on Day 168 (week 24)

Camcevi 21 mg led to a marked reduction in serum PSA levels from baseline after the first injection, which was maintained until end of study in both ITT and PP populations. Mean PSA levels decreased substantially by Day 84, with wide baseline variability reflecting heterogeneity of the study population. No increase in PSA levels towards end of study was observed, and fewer than 2% of subjects experienced PSA relapse by Day 168, supporting the conclusion that Camcevi 21 mg effectively reduces and maintains suppression of serum PSA levels.

Secondary endpoint 3: The effect of Camcevi 21 mg on change of serum LH levels

The administration of Camcevi 21 mg with three 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. An acute and transient increase of mean serum LH levels was observed after each administration of Camcevi 21 mg. In the MAA of Camcevi 42 mg, 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 latter was not observed in the current study FP01C-17-001 for Camcevi 21 mg.

[25] Gomella LG, Effective testosterone suppression for prostate cancer: is there a best castration therapy? Rev Urol. 2009; 11(2):52-60.
[26] EAU Guidelines Prostate Cancer, updated 2025, EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

Secondary endpoint 4: The percentage of subjects with enhanced serum testosterone concentration suppression to ≤ 20 ng/dL on Day 28 (week 4) and on Day 168 (week 24)

Concerning the data on patients with testosterone surges above the more stringent level of 20 ng/dL, 72% of patients (103/143) in the ITT population and 71.2% (94/132) in the PP population had testosterone levels ≤ 20 ng/dL. On Day 168, the percentage of subjects with serum testosterone level ≤ 20 ng/ dL was 96.4% (135/140) in the ITT population and 96.2% (125/130) in the PP population. The suppression of testosterone appeared to gradually deepen over time also based on more detailed listings provided in the submission

Regarding the more stringent suppression level of testosterone, no comparative data and discussion if Camcevi 21 mg mg and Eligard 22.5 mg were comparable towards the EOS were provided However, this doesn't not impact the assessment of the current procedure because it was only supportive data for Eligard 22.5 mg.

Ancillary analyses

Predefined and post-hoc subgroup analyses and sensitivity analyses

No subgroup analysis was performed in Study FP01C-17-001 on Camcevi 21 mg.

The Applicant conducted post-hoc analyses of FP01C-17-001 to re-assess serum testosterone suppression by thresholds (< 50 ng/dL, < 20 ng/dL) to align with the recent FDA Guidance on GnRH Analogues in Prostate Cancer (2022)[27], which recommends castrate thresholds of < 50 ng/dL and < 20 ng/dL. Re-assessments were carried out and completed in the primary efficacy analysis set, the ITT population (N=144), where serum testosterone level was > 50 ng/dL in 98.6% of subjects by Day 28 and 97.9% in subjects from Day 8 through Day 168. The percentages are the same as for the protocol-specified ≤ 50 ng/dL. It is concluded that Camcevi 21 mg suppressed the testosterone levels effectively and maintained them suppressed throughout the study.

Pre-defined sensitivity analyses were performed for serum testosterone levels ≤ 50 ng/dL. Post hoc sensitivity analysis showed that Camcevi 21 mg suppressed serum testosterone concentrations to < 50 ng/dL even if missing values previously handled as censored as specified in the protocol of study FP01C-17-001 were alternatively handled as therapeutic failures. A further sensitivity analysis taking the approach of handling dropouts and subjects with consecutive missing values as treatment failures, irrespective of serum testosterone levels before and after missing time points, showed that Camcevi 21 mg effectively suppressed serum testosterone concentrations to < 50 ng/dL. Two additional sensitivity analyses considering co-medications potentially interfering with serum testosterone levels (respective subjects either considered treatment failures / censored or excluded from analysis) and the potential impact on the primary efficacy endpoint (serum testosterone suppression < 50 ng/dL) showed that Camcevi 21 mg effectively suppressing serum testosterone below the castrate threshold. This analysis revealed no discordance in overall primary efficacy endpoint outcomes between the different approaches of handling missing values.

Results in special populations

The majority (72%, 103/144) of the patients were 65–84 years old and only 4 patients were older than 85 years. Serum leuprorelin peak levels and overall exposure were higher in subjects aged > 79 years compared to subjects aged < 60 years, while remaining within the therapeutic window (0.2 to 2 ng/mL). Median serum testosterone concentration time profiles were comparable among

[27] FDA Guidance GnRH Analogues in Prostate Cancer. Advanced Prostate Cancer: Developing Gonadotropin-Releasing Hormone Analogues. Guidance for Industry; U.S. Department of Health and Human Services, Food and Drug Administration; Center for Drug Evaluation and Research (CDER), Oncology Center of Excellence (OCE); May 2022. https://www.fda.gov/media/129027/download

age categories. Serum testosterone suppression most pronounced in in the > 79 years age group. These findings do not indicate needs to amend the SmPC text, also considering the current SmPC for Eligard 22.5 mg.

Patients with renal and hepatic impairment were included in the study with the same bilirubin, AST, ALT, and serum creatinine limits as in the study for Camcevi 42 mg. Regarding renal impairment, no information on chronic kidney disease stage according to the KDIGO definition was collected. By eGFR, there were 93 patients with mild, 7 patients with moderate, and no patients with severe renal impairment. The number of patients with moderate (7/144) or severe (0/144) renal impairment is too low to allow meaningful conclusions. No new efficacy emerged regarding the effect of Camcevi 21 mg to suppress serum testosterone and PSA levels in renal impairment. The evaluation of hepatic impairment was limited due to the small number of affected subjects and the absence of data pertaining to Child-Pugh classification. A retrospective review of medical histories identified six subjects with potential hepatic impairment, based on preferred terms including Alcoholic liver disease, Cholelithiasis, Hepatic cyst, Hepatic steatosis, Hyperbilirubinaemia, and Liver disorder. Only one subject demonstrated elevated liver enzyme levels at Day 28. Given the limited dataset and lack of formal hepatic function stratification, no definitive conclusions can be drawn regarding hepatic impact. However, no new efficacy concerns were identified in relation to hepatic status.

Supportive studies

The Applicant conducted a PubMed literature search on the 25th August 2024 using terms leuprolide depot, 3-month (and related synonyms), and prostate cancer to identify relevant clinical studies for 3-monthly administered 22.5 mg leuprolide products. The justification for both inclusion and exclusion of studies is adequately described, and the criteria applied are reasonable and consistent with the objective of identifying clinical efficacy evidence for 3-monthly leuprolide 22.5 mg depot formulations. An updated search conducted on the 4th December 2025 using the same criteria did not identify any additional publications. In the literature search, a total of 15 relevant clinical studies, including the main clinical studies supporting Lupron Depot 22.5 mg and Eligard 22.5 mg were identified. 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. This conclusion can be generally agreed.

The proposed wording of the indications for Camcevi 21 mg is the same as for Camcevi 42 mg: "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" and also the same as for Eligard 22.5 mg. The proposed indication is considered acceptable because it covers the same patient groups as the reference product's indication and the study FP01C-17-001, and there is relevant use in these patient groups.

5.3.9.2. Conclusions on the clinical efficacy

Results from study FP01C-17-001 showed that Camcevi 21 mg effectively suppressed serum testosterone levels to castrate levels (≤ 50 ng/dL) by Day 28 in 98.6% of patients in the ITT population and maintained suppression through Day 168. The administration of Camcevi 21 mg significantly reduced serum PSA levels from baseline until the end of the study. The SmPC wording is the same as in the SmPC for Camcevi 42 mg and only the information concerning study with Camcevi 21 mg (FP01C-17-001) have been added.

The MAA is approvable from the efficacy point of view.

5.4. Clinical safety

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse Drug Reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

The Applicant provides a clinical safety database for Camcevi 21 mg consisting of the following information:

1. Safety and tolerability data obtained in the main clinical Phase 3 single-arm 24-week study FP01C-17-001 comprising 144 enrolled subjects with advanced prostate cancer in need for ADT.
2. Previous findings on safety and tolerability for approved leuprorelin products as laid down in respective labelling, in particular for the Lupron 1 mg (Lupron injection) and its depot product successors.
3. Supportive safety data from patients with advanced prostate cancer in need for ADT treated with other 3-month leuprorelin depot forms in published clinical studies.Please see supportive studies in previous sections.
4. Post marketing information gained with Camcevi 42 mg following the first commercialization of Camcevi 42 mg in the US in May 2021 as well as safety / tolerability outcomes obtained in the main study FP01C-13-001 (EMEA/H/C/005034).

5.4.2. Patient exposure

Please, see the description of the clinical study contributing to safety in *Table 24*.

Study FP01C-17-001

The safety analysis set, defined as any subject who received a dose of Camcevi 21 mg, comprised all subjects enrolled in main clinical Study FP01C-17-001 (N=144).

The clinical trial start date (first patient enrolled) for FP01C-17-001 was 26th September 2017 and the clinical trial end date was 2nd September 2019. The last patient completed 19th November 2018. Of all 144 subjects enrolled, 12 (8.33%) did not receive the second dose of Camcevi 21 mg. All other subjects received 2 doses, covering a treatment period of 24 weeks for a drug designed to be administered once every 12 weeks (3 months). Of the 144 enrolled subjects, 15 (10.4%) subjects did not complete the study, including one subject who terminated early due to AE / SAE (stroke; unrelated to Camcevi 21 mg).

Summary of subject demographics and baseline characteristics in study FP01C-17-001 is presented in *Table 24* and main clinically relevant comorbidities in Table 36.

Table 29: Main clinically relevant comorbidities

Comorbidity	**Number of Patients (n)**	**Percentage (%)**
Hypertension	77	53.47%
Essential Hypertension	24	16.67%
Type 2 diabetes mellitus	23	15.97%
Hyperlipidemia	13	(9.03%)
Hypercholesterolaemia	17	(11.81%)
Coronary Artery Disease	3	2.08%
Chronic Kidney Disease	2	1.3%

Table 30: Patient exposure to Camcevi 21 mg (cut off for FP01C-17-001, 2nd September 2019)

	Patients enrolled	Patients exposed*	Patients exposed to the proposed dose range	Patients with long term** safety data
Blinded studies (placebo-controlled)	NA	NA	NA	NA
Blinded studies (active -controlled)	NA	NA	NA	NA
Open studies -FP01C-17-001		144	144	No data for longer than 6 months exposure exist (2 SC injections, 3 months apart)
Post marketing	NA	NA	NA	There is no post marketing data on Camcevi 21 mg. Post marketing data on Camcevi 42 mg is presented in 5.4.10.
Compassionate use	NA	NA	NA	

* Received at least 1 dose of active treatment
** In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.
NA = not applicable

Published Studies on 3-Month Depot Leuprorelin Forms

A total of 15 studies (comprising 13 primary articles and 2 subgroup analyses) from the published literature were identified in support of 3-month leuprorelin depot forms in the treatment of prostate cancer, including the main studies supporting efficacy and safety of Lupron Depot 22.5 mg and Eligard 22.5 mg. In the 13 primary studies, 2,728 patients with prostate cancer were exposed to 22.5 mg of 3-month leuprolide (acetate) depot for up to 3 years with follow-up of up to 5 years. Studies in the published literature were conducted mainly in the US and Europe. All were conducted in an adult prostate cancer population. An exact number of geriatric subjects cannot be calculated, but all 13 primary studies were conducted in adults with a mean age > 65 years old, except in 1 study where data were not provided. Six studies (2079 subjects) used a SC injection, while seven studies (649 subjects) used an IM injection.

6-Month Depot Leuprorelin Mesilate Depot Form Camcevi 42 mg

Of the 137 subjects enrolled in main clinical study FP01C-13-001 for Camcevi 42 mg (EMEA/H/C/005034; Camcevi SmPC, 2024), the average age was 71.1 ± 8.7 years, and all were adult males. Thirty subjects from FP01C-13-001 enrolled into the safety extension study FP01C-13001-EX.

5.4.3. Adverse events

Table 31: Summary of treatment-emergent AEs (study FP01C-17-001; full analysis set)

Variable/ Status		Safety Population (N=144)		
		Event	Subject	
		E	n	%
Subjects with any TEAE		217	90	(62.50%)
Subjects with any drug-related TEAE		88	53	(36.81%)
TEAEs by severity				
	Grade 1 (Mild)	165	79	(87.78%)
	Grade 2 (Moderate)	43	28	(31.11%)
	Grade 3 (Severe)	9	7	(7.78%)
	Grade 4 (Life-threatening)	0	0	(0%)
	Grade 5 (Death)	0	0	(0%)
TEAEs by relationship				
	Definite	37	31	(34.44%)
	Possible	51	33	(36.67%)
	Unrelated	129	64	(71.11%)
Serious TEAE				
	No	207	85	(94.44%)
	Yes	10	9	(10%)
Drug-related TEAE by severity				
	Grade 1 (Mild)	74	50	(55.56%)
	Grade 2 (Moderate)	14	12	(13.33%)
	Grade 3 (Severe)	0	0	(0%)
	Grade 4 (Life-threatening)	0	0	(0%)
	Grade 5 (Death)	0	0	(0%)

TEAE = treatment-emergent adverse event
Note:
[E is event number, n is number of subjects with event, and the rate is defined as: 100%*The number of subjects with event in the category (n) / The number of subjects with event (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 is combined as one AE with the maximum severity/relationship category for analysis.]

Table 32: Summary of AEs by MeDRA SOC (study FP01C-17-001)

	Safety Population (N=144)		
	Event	Subject	
System Organ Class	E	n	%
All Body Systems	**217**	**90**	**(62.50%)**
Vascular disorders	58	47	(32.64%)
Investigations	30	22	(15.28%)
General disorders and administration site conditions	22	19	(13.19%)
Infections and infestations	19	17	(11.81%)
Musculoskeletal and connective tissue disorders	30	17	(11.81%)
Renal and urinary disorders	12	12	(8.33%)
Injury, poisoning and procedural complications	7	5	(3.47%)

	Safety Population (N=144)		
	Event	Subject	
System Organ Class	E	n	%
Cardiac disorders	6	5	(3.47%)
Gastrointestinal disorders	5	5	(3.47%)
Nervous system disorders	5	4	(2.78%)
Metabolism and nutrition disorders	4	4	(2.78%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	3	(2.08%)
Surgical and medical procedures	4	3	(2.08%)
Psychiatric disorders	3	3	(2.08%)
Respiratory, thoracic and mediastinal disorders	3	3	(2.08%)
Skin and subcutaneous tissue disorders	2	2	(1.39%)
Eye disorders	1	1	(0.69%)
Hepatobiliary disorders	1	1	(0.69%)
Reproductive and breast disorders	1	1	(0.69%)
Note: [MedDRA version is 21.1.] [E is event number, n is number of subjects with event, and the SAE incidence rate: 100%*The number of subjects with event (n) / The number of subjects in the safety population (N)] [For subject with the same AE but multiple different severity/relationship, the multiple events are combined as one AE with the maximum severity/relationship category for analysis.]			

Table 33: Treatment-emergent AEs (by preferred term) with greater than or equal 5% frequency (study FP01C-17-001)

	Safety Population (N=144)		
	Event	Subject	
Preferred Term	E	n	%
Hot flush	35	35	(24.31%)
Hypertension	18	16	(11.11%)
Weight increased	11	11	(7.64%)
Injection site haemorrhage	9	8	(5.56%)
Note: [The MedDRA version is 21.1] [E is event number, n is number of subjects with event, and the AE incidence rate: 100%*The number of subjects with event (n) / The number of subjects in the 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 is combined as one AE with the maximum severity/relationship category for analysis].			

Table 34: Drug-related AEs (by preferred term) with greater than or equal 5% frequency (study FP01C-17-001)

	Safety Population (N=144)		
	Event	Subject	
Preferred Term	E	n	%
Hot flush	34	34	(23.61%)
Weight increased	11	11	(7.64%)
Hypertension	11	9	(6.25%)
Injection site haemorrhage	9	8	(5.56%)
Note: [The MedDRA version is 21.1] [E is event number, n is number of subjects with event, and the AE incidence rate: 100%*The number of subjects with event (n) / The number of subjects in the safety population (N)] [Relationship to Study Drug: AEs related to study drug include AEs classified as 'Definite', 'Possible' or missing relationship. AEs not related to study drug include AEs that are 'Unrelated'.]			

[For subject with the same AE but multiple different severity/relationship, the multiple events are combined as one AE with the maximum severity/relationship category for analysis.]

Published studies on 3-month depot leuprorelin forms

Publications that presented data for 3-month leuprorelin acetate depot formulations were identified and reviewed for potential safety findings. Most AEs were mild or moderate in severity. The most commonly reported AEs included injection site reactions (including hematoma, burning, pain, and erythema), hot flushes, and fatigue.

AEs assessed as related to treatment, where specifically denoted, were most commonly hot flash/flush, fatigue, injection site pain, and anaemia.

6-month leuprorelin mesilate depot form Camcevi 42 mg

Overall, the most common AEs reported in study FP01C-13-001 (EMEA/H/C/005034; Camcevi SmPC, 2024 and Shore et al., 2020) were hot flush (reported in 48.9% of subjects), followed by hypertension (14.6%), pain in extremity (9.5%), injection site pain (7.3%), arthralgia (6.6%), fatigue (6.6%), nocturia (5.8%), back pain (5.1%), and nasopharyngitis (5.1%). Most AEs were mild or moderate.

5.4.3.1. Adverse drug reactions

Table 35: Drug-related treatment-emergent adverse events by severity – MedDRA (safety population)

		Safety Population (N=144)		
		Event	Subject	
	Severity System Organ Class / Preferred Term	E	n	%
Grade 1 (Mild)				
ALL BODY SYSTEM				
	OVERALL	74	50	(34.72%)
General disorders and administration site conditions				
	- Overall	19	16	(11.11%)
	Asthenia	1	1	(0.69%)
	Injection site erythema	2	2	(1.39%)
	Injection site haemorrhage	9	8	(5.56%)
	Injection site induration	1	1	(0.69%)
	Injection site nodule	3	2	(1.39%)
	Injection site pain	1	1	(0.69%)
	Injection site reaction	1	1	(0.69%)
	Localised oedema	1	1	(0.69%)
Injury, poisoning and procedural complications				
	- Overall	3	2	(1.39%)
	Post procedural complication	3	2	(1.39%)
Investigations				
	- Overall	13	12	(8.33%)
	Alanine aminotransferase increased	1	1	(0.69%)
	Aspartate aminotransferase increased	1	1	(0.69%)
	Electrocardiogram QT prolonged	1	1	(0.69%)
	Weight increased	10	10	(6.94%)

	Safety Population (N=144)		
	Event	Subject	
Severity System Organ Class / Preferred Term	E	n	%
Metabolism and nutrition disorders			
- Overall	1	1	(0.69%)
Decreased appetite	1	1	(0.69%)
Musculoskeletal and connective tissue disorders			
- Overall	1	1	(0.69%)
Pain in extremity	1	1	(0.69%)
Psychiatric disorders			
- Overall	2	2	(1.39%)
Insomnia	1	1	(0.69%)
Libido decreased	1	1	(0.69%)
Renal and urinary disorders			
- Overall	1	1	(0.69%)
Pollakiuria	1	1	(0.69%)
Skin and subcutaneous tissue disorders			
- Overall	1	1	(0.69%)
Hyperhidrosis	1	1	(0.69%)
Vascular disorders			
- Overall	33	33	(22.92%)
Flushing	1	1	(0.69%)
Hot flush	32	32	(22.22%)
Grade 2 (Moderate)			
ALL BODY SYSTEM			
OVERALL	14	12	(8.33%)
Investigations			
- Overall	1	1	(0.69%)
Weight increased	1	1	(0.69%)
Vascular disorders			
- Overall	13	11	(7.64%)
Hot flush	2	2	(1.39%)
Hypertension	11	9	(6.25%)

Note:The MedDRA version is 21.1.
E is event number, n is number of subjects with event, and the AE incidence rate: 100%*The number of subjects with event (n) / The number of subjects in the 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 is combined as one AE with the maximum severity/relationship category for analysis.

Published studies on 3-month depot leuprorelin forms

AEs assessed as related to treatment were most commonly hot flash/flush, fatigue, injection site pain, and anaemia.

6-month depot leuprorelin mesilate depot form Camcevi 42 mg

No new ADRs were identified in the main study compared to those already reported in the SmPC for Camcevi 42 mg.

5.4.3.1.1. Adverse drug reactions in the SmPC

Table 36 Undesirable effects reported for leuprorelin-containing medicinal products for injection

Infections and infestations	
common	nasopharyngitis
uncommon	urinary tract infection, local skin infection
Blood and lymphatic system disorders	
common	haematology changes, anaemia
Metabolism and nutrition disorders	
uncommon	aggravated diabetes mellitus
Psychiatric disorders	
uncommon	abnormal dreams, depression, decreased libido
Nervous system disorders	
uncommon	dizziness, headache, hypoaesthesia, insomnia, taste disturbance, smell disturbance, vertigo
rare	abnormal involuntary movements
not known	idiopathic intracranial hypertension (pseudotumor cerebri) (see section 4.4)
Cardiac disorders	
uncommon	QT prolongation (see sections 4.4 and 4.5), myocardial infarction (see section 4.4)
Vascular disorders	
very common	hot flashes
uncommon	hypertension, hypotension
rare	syncope, collapse
Respiratory, thoracic and mediastinal disorders	
uncommon	rhinorrhoea, dyspnoea
not known	interstitial lung disease
Gastrointestinal disorders	
common	nausea, diarrhoea, gastroenteritis/colitis
uncommon	constipation, dry mouth, dyspepsia, vomiting
rare	flatulence, eructation
Skin and subcutaneous tissue disorders	
very common	ecchymoses, erythema
common	pruritus, night sweats
uncommon	clamminess, increased sweating
rare	alopecia, skin eruption
Not known	Stevens-Johnson syndrome/Toxic Epidermal Necrolysis (SJS/TEN) (see section 4.4) Toxic Skin Eruption Erythema Multiforme
Musculoskeletal and connective tissues disorders	
common	arthralgia, limb pain, myalgia, rigors, weakness
uncommon	back pain, muscle cramps
Renal and urinary disorders	
common	urinary infrequency, difficulty in micturation, dysuria, nocturia, oliguria
uncommon	bladder spasm, haematuria, aggravated urinary frequency, urinary retention
Reproductive system and breast disorders	
common	breast tenderness, testicular atrophy, testicular pain, infertility, breast hypertrophy, erectile dysfunction, reduced penis size
uncommon	gynaecomastia, impotence, testicular disorder
rare	breast pain
General disorders and administration site conditions	
very common	fatigue, injection site burning, injection site paraesthesia
common	malaise, injection site pain, injection site bruising, injection site stinging
uncommon	injection site pruritus, injection site induration, lethargy, pain, pyrexia
rare	injection site ulceration
very rare	injection site necrosis
Investigations	
common	increased blood creatinine phosphokinase, prolonged coagulation time
uncommon	increased alanine aminotransferase, increased blood triglycerides, prolonged prothrombin time, increased weight

5.4.4. AEs of special interest, serious adverse events and deaths, other significant events

AEs of special interest

AEs of special interest in the study FP01C-17-001 were injection site reaction, bone and urinary pain, urinary signs and symptoms.

Local skin tolerability

All the reported local injection site reactions were only mild in severity and were resolved by the EOS. No subjects had moderate or severe local injection site intolerances.

Bone pain

No statistically significant change was observed in bone pain assessments from Day 0 to Day 168 (EOS).

Urinary signs and symptoms, quality of life

The degree of urinary signs and symptoms was assessed per questionnaire including questions on urinary signs, one question on urinary symptoms, and total I-PSS score (please, see also 5.3.7. According to the Applicant, the results suggested that two separate doses of Camcevi 21 mg did not seem to cause additional or worsened urination symptoms in the subjects. Most subjects felt "delighted/pleased/mostly satisfied" at baseline (75%) and on Day 168 (82%).

On Day 168 compared to baseline, approximately 30.2% of subjects felt that their current living conditions were improved, 52.5% of subjects felt that their current living conditions were unchanged, and 17.3% of subjects felt their current living conditions worsened. There was a statistically significant decrease in I-PSS score on Day 168 noted (mean ±SD change -1.2±4.8, p=0.0069), indicating improvement.

Deaths

Sponsor-conducted study FP01C-17-001

No deaths were reported in study FP01C-17-001.

Published studies on 3-month depot leuprorelin forms

Five studies representing a combined 3,437 subjects treated with leuprorelin depot reported deaths during the treatment period within varying amounts of follow-up time ranging from approximately 4 months to 5 years. A study in 1906 subjects reported 14 deaths (0.7%) within 12 months of follow-up (Ohlmann and Gross-Langenhoff 2018). A study in 932 subjects reported 86 deaths (9.2%) within 5 years of follow up (Schulman et al. 2016). A study in 250 subjects reported 1 death (Spry et al., 2006, Spry et al., 2009). A study in 243 subjects reported 2 deaths (0.8%) (Braeckman and Michielsen 2014). A study in 106 subjects reported 8 deaths (7.5%) within 15 months of follow-up; however, no further details were stated regarding the circumstances or relation to study drug (Malek et al., 2022). Among all studies where causality assessments were provided, all deaths were reported as unrelated to study treatment.

6-Month leuprorelin mesilate depot form Camcevi 42 mg

In FP01C-13-001 (EMEA/H/C/005034; Camcevi SmPC, 2024 and Shore et al., 2020), 3 deaths were reported (representing 2.2% of subjects). The causes of death included cerebrovascular accident, pulmonary embolism, and metastatic prostate cancer to lungs and acute kidney injury. All fatal events were determined to be unrelated to study drug.

Other SAEs

There were 10 SAEs reported in 9 subjects in main clinical Study FP01C-17-001. A listing of the reported SAEs is provided in Table 43. All SAEs were assessed as unrelated to study drug by the investigator.

Table 37 Listing of SAEs (Study FP01C-17-001)

Subject No.	AE by Preferred Term	Onset Date	Resolution Date	Severity Grade	Relationship to Study Drug	Action Taken	Treatment Required	Outcome / Ongoing
LT01-014	Acute myocardial infarction	2018-06-10	2018-06-15	3	Unrelated	Dose not changed	Yes	Resolved
	Rehabilitation therapy	2018-06-18	2018-07-05	2	Unrelated	Dose not changed	No	Resolved
LT02-020	Tendon rupture	2018-06-05	2018-06-08	2	Unrelated	Dose not changed	Yes	Ongoing
LT02-022	Basal cell carcinoma	2018-07-23	2018-07-23	2	Unrelated	Dose not changed	Yes	Ongoing
LT03-008	Drug-induced liver injury	2018-02-13	2018-02-15	1	Unrelated	Dose not changed	No	Ongoing
LT03-014	Pancreatitis acute	2018-06-21	2018-08-27	2	Unrelated	Not Applicable	Yes	Resolved
LT04-009	Urethral stenosis	2017-12-18	2017-12-21	3	Unrelated	Dose not changed	Yes	Resolved with sequelae
LT04-022	Cerebrovascular accident	2018-08-03	2018-11-01	3	Unrelated	Drug withdrawn	Yes	Resolved with sequelae
SK01-002	Sciatica	2018-02-19	2018-02-26	3	Unrelated	Dose not changed	Yes	Resolved with sequelae
SK02-014	Oropharyngeal neoplasm	2018-03-26	N/A	2	Unrelated	Dose not changed	Yes	Not Resolved
MedDRA version 21.1. Severity categories: 1 = mild, 2 = moderate, 3 = severe								

Published studies on 3-month depot leuprorelin forms

SAEs were assessed among 7 studies in 2,010 subjects with 3-month leuprorelin acetate depot products. Several studies, comprising the majority of subjects exposed, reported rates of SAEs among treated subjects between 0.8% and 29.2% but did not otherwise provide details; the majority of studies noted that most or all SAEs were considered unrelated to study drug (Malek et al., 2022, Shore et al., 2019, Schulman et al., 2016, Chu et al., 2002. Additionally, one study in 243 subjects reported SAEs in 2 subjects (1 syncope and 1 prostatic obstruction, both unrelated to study drug) (Braeckman and Michielsen 2014). In another study comparing leuprorelin monotherapy (n=22) to leuprorelin and pamidronate combination therapy (n=21), SAEs were reported in 8 subjects total: 3 (14%) of leuprorelin treated subjects including delirium, gastric cancer, and haematuria; and 5 (24%) of leuprorelin and pamidronate treated subjects including colon cancer, cystitis, hepatic angiosarcoma, lymphoma, and memory disorder (Smith et al., 2001)[31]. Related SAEs were noted in 2 studies and included musculoskeletal chest pain and femur fracture (Malek et al., 2022) and increase in PSA and metastases to bone (Ohlmann and Gross-Langenhoff 2018).

6-month leuprorelin mesilate depot form Camcevi 42 mg

There were 34 SAEs reported in 20 subjects in FP01C-13-001 (EMEA/H/C/005034; and Shore et al., 2020). The only SAE that occurred in more than 1 subject was subdural hematoma (N=2 subjects, 1.5% of total). Of the 34 SAEs, only 3 (1 per subject) were determined to be related to Camcevi 42 mg by the investigators. These included blurred vision, left hip fracture, and myocardial infarction.

There were 7 new SAEs reported in 4 subjects in safety extension Study FP01C-13-001-EX. These SAEs by preferred term were deep vein thrombosis, dyspnea, hip fracture, knee arthroplasty, perforated ulcer,

pyelonephritis acute, and sepsis. All new SAEs were determined to be unrelated to the administration of Camcevi 42 mg by the investigators.

5.4.5. Discontinuation due to adverse events

Study FP01C-17-001

There were one subject (1/144, 0.7%) who experienced AEs (stroke) that led to premature discontinuation. This event was determined to be unrelated to the Camcevi 21 mg by investigators.

Published studies on 3-month depot leuprorelin forms

Four clinical studies with total of 1424 patients reported that 0–10.4% of subjects discontinued treatment due to an AE, though it was not always specified whether the AE was considered treatment related.

6-Month depot leuprorelin mesilate depot form Camcevi 42 mg

In FP01C-13-001 (EMEA/H/C/005034; Camcevi SmPC, 2024 and Shore et al., 2020), there were 5 subjects (3.6%) who experienced 6 AEs that led to premature discontinuation: acute kidney injury, atrial fibrillation, cerebrovascular accident, death, hormone refractory prostate cancer, and prostate cancer metastatic. All events were determined to be unrelated to Camcevi 42 mg.

In extension Study FP01C-13-001-EX (EMEA/H/C/005034; Camcevi SmPC, 2024), there were no AEs that led to discontinuation. All other significant AEs, including deep vein thrombosis, dyspnea, hip fracture, knee arthroplasty, perforated ulcer, pyelonephritis acute, and sepsis (all 1 subject each) were unrelated to the administration of Camcevi 42 mg

5.4.6. Safety in special populations

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.

Renal and hepatic impairment

The PK of Camcevi 21 mg in subjects with renal or hepatic impairment has not been investigated.

Elderly

Table 38: AEs by age range

	Active			
MedDRA Terms	Age <65 years (N=37) n (%)	Age 65-74 years (N=63) n (%)	Age 75-84 years (N=40) n (%)	Age ≥85 years (N=4) n (%)
Total AEs	18 (48.65%)	45 (71.43%)	25 (62.50%)	2 (50.00%)
Serious AEs – Total	2 (5.41%)	4 (6.35%)	3 (7.50%)	0 (0%)
- Fatal	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Hospitalization/prolong existing hospitalization	2 (5.41%)	4 (6.35%)	3 (7.50%)	0 (0%)
- Life-threatening	0 (0%)	0 (0%)	0 (0%)	0 (0%)

	Active			
MedDRA Terms	Age <65 years (N=37) n (%)	Age 65-74 years (N=63) n (%)	Age 75-84 years (N=40) n (%)	Age ≥85 years (N=4) n (%)
- Disability/incapacity	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Other (medically significant)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AE leading to drop-out	0 (0%)	0 (0%)	1 (2.5%)	0 (0%)
Psychiatric disorders	2 (5.41%)	0 (0.0%)	1 (2.50%)	0 (0.0%)
Nervous system disorders	0 (0.0%)	2 (3.17%)	2 (5%)	0 (0.0%)
Injury, poisoning, and procedural complications	1 (2.70%)	4 (6.35%)	0 (0.0%)	0 (0.0%)
Cardiac disorders	0 (0.0%)	3 (4.76%)	2 (5%)	0 (0.0%)
Vascular disorders	11 (29.73%)	24 (38.10%)	11 (27.50%)	1 (25%)
Cerebrovascular disorders	NA	NA	NA	NA
Infections and infestations	3 (8.11%)	8 (12.70%)	6 (15%)	0 (0.0%)
Anticholinergic syndrome	NA	NA	NA	NA
Quality of life decreased	NA	NA	NA	NA
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	NA	NA	NA	NA

NA = not applicable

Table 39: AE by special population

	Active				Comparator			
MedDRA Terms	Hepatically impaired* n = 6 (6/144 4.2%)	Renally impaired** n = 20 (20/144 23.9%)	Pregnant n (%)	Other n (%)	Hepatically impaired* n (%)	Renally impaired** n (%)	Pregnant n (%)	Other n (%)
Total AEs	5 (83.33 %)	15 (75%)	NA	NA	NA	NA	NA	NA
Serious AEs – Total	0 (%)	1 (5%)	NA	NA	NA	NA	NA	NA
- Fatal		0 (%)	NA	NA	NA	NA	NA	NA

	Active				Comparator			
MedDRA Terms	Hepatically impaired* n = 6 (6/144 4.2%)	Renally impaired** n = 20 (20/144 23.9%)	Pregnant n (%)	Other n (%)	Hepatically impaired* n (%)	Renally impaired** n (%)	Pregnant n (%)	Other n (%)
- Hospitalization/prolong existing hospitalization	NA	1 (5%)	NA	NA	NA	NA	NA	NA
- Life-threatening	NA	0 (%)	NA	NA	NA	NA	NA	NA
- Disability/incapacity	NA	0 (%)	NA	NA	NA	NA	NA	NA
- Other (medically significant)	NA	0 (%)	NA	NA	NA	NA	NA	NA
AE leading to drop-out	0 (%)	0 (%)	NA	NA	NA	NA	NA	NA

* The hepatically impaired medical histories were derived from the following preferred terms: Alcoholic liver disease, Cholelithiasis, Hepatic cyst, Hepatic steatosis, Hyperbilirubinaemia and Liver disorder.
** The renally impaired medical histories were derived from the following preferred terms: Chronic kidney disease, Diabetic nephropathy, Dysuria, Haematuria, Nephrolithiasis, Nephrosclerosis, Neurogenic bladder, Nocturia, Renal cyst, Renal impairment and Urinary retention.

5.4.7. Immunological events

No information is available. Camcevi 21 mg is not expected to result in major immunological events and hence the issue can be considered not relevant.

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

No pharmacokinetic drug-drug interaction studies have been performed. Drug-drug interactions known to prolong QT interval or to induce *Torsade de pointes* are described in the SmPC. These are based on the dataset of FP01C-13-001 on Camcevi 42 mg and the SmPCs of Eligard 45 mg, Eligard 22.5 mg, and Eligard 7.5 mg.

5.4.9. Vital signs and laboratory findings

Study FP01C-17-001

Vital signs and physical findings

Statistically significant changes from baseline ($p<0.05$) were observed in some vital signs on Day 168 relative to baseline, including the following: increase in mean weight (kg) (mean ±SD change 0.85±3.05, $p<0.0001$), decrease in systolic blood pressure (mmHg) (mean ±SD change -2.4±11.71, $p=0.0189$), and decrease in heart rate (/min) (mean ±SD change 3.1±9.41, $p=0.0002$). Physical examination results were normal in most subjects during the study.

ECG

A few abnormalities in ECG findings were observed in several subjects during the study period, with most subjects showing no clinically significant overall ECG findings.

Additional PK/ECG analyses revealed that the standard clinical dose of Camcevi 21 mg reduced testosterone to castrated levels with no meaningful change in the ECG except for the expected increase in QTcF, which was consistent with the known effect of sex hormones on QT (Oskui et al., 2013).

Laboratory findings

Haematology

Haematological parameters determined included haemoglobin, haematocrit, RBCs, WBCs, platelets, neutrophils, eosinophils, basophils, lymphocytes, monocytes, and HbA1c. Statistically significant changes between baseline and Day 168 (EOS) were observed, including decreases of mean haemoglobin, haematocrit, RBCs, and neutrophils and increase of mean lymphocyte counts. None of these changes was judged clinically significant by investigators.

Biochemistry

Statistically significant changes between baseline and Day 168 (EOS) were observed for several biochemical parameters, including increases of mean ALT, AST, alkaline phosphatase, blood urea nitrogen, sodium, calcium, phosphorus, high-density lipoprotein, and triglycerides levels and decreases of mean total bilirubin, serum creatinine, and magnesium levels.

One subject was reported to have abnormally high AST and ALT levels on Day 168. This abnormal finding was possibly related to Camcevi 21 mg dosing as judged by the investigator. Abnormal blood glucose levels in one subject were due to pre-existing Type II diabetes mellitus and assessed as not related to Camcevi 21 mg dosing.

Table 40: Summary of clinical laboratory results

Variable	Visit	Statistics	Safety Population (N=144)
ALT (U/L)	Baseline	n	144
		Mean (SD)	21.5 (9.70)
		Median (min, max)	19 (6, 65)
		Hodges-Lehmann estimator	20.0
		95% CI	(19.95, 23.15)
		Normal	140 (97.2 %)
		Abnormal NCS	4 (2.78 %)
	Day 168 (V22/EOS)	n	140
		Mean (SD)	27.0 (17.66)
		Median (min, max)	22 (8, 145)
		Hodges-Lehmann estimator	24.0
		95% CI	(24.01, 29.92)
		Normal	122 (87.1 %)
		Abnormal NCS	16 (11.4 %)
		Abnormal CS	2 (1.43 %)
	Change at Day 168 (V22/EOS)	n	140
		Mean (SD)	5.4 (14.17)
		Median (min, max)	3 (-22, 103)
		Hodges-Lehmann estimator	4.0
		95% CI	(3.05, 7.78)
		P-value*	<0.0001
AST (U/L)	Baseline	n	144
		Mean (SD)	21.6 (7.29)
		Median (min, max)	20 (9, 56)
		Hodges-Lehmann estimator	20.5

		95% CI	(20.38, 22.78)
		Normal	137 (95.1 %)
		Abnormal NCS	7 (4.86 %)
	Day 168 (V22/EOS)	n	140
		Mean (SD)	24.7 (11.33)
		Median (min, max)	22.5 (14, 116)
		Hodges-Lehmann estimator	23.0
		95% CI	(22.84, 26.62)
		Normal	130 (92.9 %)
		Abnormal NCS	8 (5.71 %)
		Abnormal CS	2 (1.43 %)
	Change at Day 168 (V22/EOS)	n	140
		Mean (SD)	3.2 (10.16)
		Median (min, max)	2 (-26, 87)
		Hodges-Lehmann estimator	2.5
		95% CI	(1.47, 4.86)
		P-value*	<0.0001
Blood glucose (mg/dL)	Baseline	n	144
		Mean (SD)	111.8 (26.84)
		Median (min, max)	104 (59, 218)
		Hodges-Lehmann estimator	107.0
		95% CI	(107.37, 116.21)
		Normal	56 (38.9 %)
		Abnormal NCS	88 (61.1 %)
	Day 168 (V22/EOS)	n	140
		Mean (SD)	113.3 (31.77)
		Median (min, max)	104 (68, 304)
		Hodges-Lehmann estimator	107.0
		95% CI	(107.94, 118.56)
		Normal	51 (36.4 %)
		Abnormal NCS	88 (62.9 %)
		Abnormal CS	1 (0.71 %)
	Change at Day 168 (V22/EOS)	n	140
		Mean (SD)	2.2 (22.99)
		Median (min, max)	0 (-70, 155)
		Hodges-Lehmann estimator	1.0
		95% CI	(-1.66, 6.02)
		P-value*	0.4390

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence interval, CS = abnormal, clinically significant, EOS = end of study, NCS = abnormal, not clinically significant, SD = standard deviation

Urinanalysis

Urinalysis included pH, specific gravity, and the presences of leukocytes, erythrocytes, nitrate, urine glucose or protein. Overall, no statistically significant change in urine pH and specific gravity was observed. One clinically significant abnormality (presence of leukocytes) was observed at the EOS in one subject.

Published studies on 3-month depot leuprorelin forms

Most published studies did not report vital signs. Two studies specifically noted that there were no clinically significant trends or changes from baseline observed in vital signs.[28,29] Weight gain, or changes in body composition following leuprorelin treatment, was addressed in a few studies. In one study of 25 subjects,

[28] Chu FM, Jayson M, Dineen MK, Perez R, Harkaway R, Tyler RC. A clinical study of 22.5 mg. La-2550: A new subcutaneous depot delivery system for leuprolide acetate for the treatment of prostate cancer. J Urol. 2002 Sep;168(3):1199-203. doi: 10.1016/S0022-5347(05)64625-3. PMID: 12187267.

[29] Shore ND, Guerrero S, Sanahuja RM, Gambús G, Parente A. A New Sustained-release, 3- Month Leuprolide Acetate Formulation Achieves and Maintains Castrate Concentrations of Testosterone in Patients With Prostate Cancer. Clin Ther. 2019 Mar;41(3):412-425. doi: 10.1016/j.clinthera.2019.01.004. Epub 2019 Feb 8. PMID: 30929678.

it was reported that mean (± SE) % fat body mass increased significantly by 4.3 ± 1.3% from baseline to week 12.[30] In another study of 43 subjects, weight gain > 5 kg was reported in 10-14% of subjects in 48 weeks of treatment.[31] A subgroup analysis of this study reported that following treatment with leuprorelin, weight increased by 2.4 + 0.8%, body fat percentage increased by 9.4 + 1.7% (driven by an increase of subcutaneous rather than intraabdominal adipose tissue), and lean body mass percentage decreased by 2.7 + 0.5% (all were statistically significant).[32]

There was no electrocardiography results discussed in the literature. Three studies addressed bone pain, urinary pain, and urinary symptoms. One study of 163 subjects reported that bone pain, urinary pain, and urinary symptoms were infrequent and remained so throughout the study; mean scores were 1.02-1.42 for all assessments (Shore et al., 2019). Another study of 117 subjects reported that patient self-assessment of bone pain, urinary symptoms, and urinary pain were low at baseline and remained unchanged during the 6-month study.[28] A third study of 94 subjects reported that bone pain and increased urinary frequency occurred in 2% of patients in 24 weeks of follow-up.[33]

Regarding health-related quality of life (QoL) In one study of 701 subjects, QoL using EORTC QLQ-C30 was comparable for the subjects treated with continuous androgen deprivation or intermittent androgen deprivation; nausea, vomiting, and appetite loss were the most distressing symptoms reported.[34] In another study of 250 subjects, it was reported that testosterone suppression led to a significant reduction in global health and QoL and deterioration in most function and symptom scales; during periods where subjects were off treatment, there was a trend of progressive improvement in health and QoL that paralleled testosterone recovery but was slower than the rate of deterioration during the treatment phase.[35]

6-month leuprorelin mesilate depot form Camcevi 42 mg

Regarding haematology, there were no clinically significant changes in the study FP01C-13-001 on Camcevi 42 mg. In the extension study FP01C-13-001-EX, one event of neutropenia was clinically significant, and it was reported as possibly related to Camcevi 42 mg. Regarding biochemical parameters assessed in the study FP01C-13-001, a few abnormal changes were found to have clinical significance, but none of them were found to be related to Camcevi 42 mg. Regarding urinalysis, a clinically significant presence of erythrocytes, leukocytes, and proteins was observed in 3 subjects during the study, but these changes were determined to not be related to Camcevi 42 mg by the investigator.

5.4.10. Post marketing experience

Camcevi 21 mg has not been approved or marketed anywhere in the world, nor has it been withdrawn from marketing/registration in any country.

[30] Smith MR, Lee H, Fallon MA, Nathan DM. Adipocytokines, obesity, and insulin resistance during combined androgen blockade for prostate cancer. Urology. 2008 Feb;71(2):318-22. doi: 10.1016/j.urology.2007.08.035. PMID: 18308111; PMCID: PMC2614378.
[31] Smith MR, McGovern FJ, Zietman AL, Fallon MA, Hayden DL, Schoenfeld DA, Kantoff PW, Finkelstein JS. Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. N Engl J Med. 2001 Sep 27;345(13):948-55. doi: 10.1056/NEJMoa010845. PMID: 11575286.
[32] Smith MR, Finkelstein JS, McGovern FJ, Zietman AL, Fallon MA, Schoenfeld DA, Kantoff PW. Changes in body composition during androgen deprivation therapy for prostate cancer. J Clin Endocrinol Metab. 2002 Feb;87(2):599-603. doi:10.1210/jcem.87.2.8299. PMID:11836291.
[33] Sharifi R, Bruskewitz RC, Gittleman MC, Graham SD Jr, Hudson PB, Stein B. Leuprolide acetate 22.5 mg 12-week depot formulation in the treatment of patients with advanced prostate cancer. Clin Ther. 1996 Jul-Aug;18(4):647-57. doi: 10.1016/s0149-2918(96)80215-3. PMID:8879893.
[34] Schulman C, Cornel E, Matveev V, Tammela TL, Schraml J, Bensadoun H, Warnack W, Persad R, Salagierski M, Gómez Veiga F, Baskin-Bey E, López B, Tombal B. Intermittent Versus Continuous Androgen Deprivation Therapy in Patients with Relapsing or Locally Advanced Prostate Cancer: A Phase 3b Randomised Study (ICELAND). Eur Urol. 2016 Apr;69(4):720-727. doi: 10.1016/j.eururo.2015.10.007. Epub 2015 Oct 29. PMID: 26520703.
[35] Spry NA, Kristjanson L, Hooton B, Hayden L, Neerhut G, Gurney H, Corica T, Korbel E, Weinstein S, McCaul K. Adverse effects to quality of life arising from treatment can recover with intermittent androgen suppression in men with prostate cancer. Eur J Cancer. 2006 May;42(8):1083-92. doi: 10.1016/j.ejca.2006.01.029. Epub 2006 May 2. PMID: 16632343.

For Camcevi 42 mg cumulative total patient exposure is estimated approximately at 29,445 patient treatment years as of 31 July 2025. Based on a review of the quarterly US periodic adverse drug experience reports through to date, no changes to the approved prescribing information for Camcevi 42 mg have been necessitated due to events reported. Currently, Camcevi 42 mg is not marketed in the EU.

The FDA Adverse Event Reporting System (FAERS) database for Q1 of 2021 through Q1 of 2024 was searched for AEs with "leuprolide acetate" or "leuprolide mesylate" being the sole keyword for the suspect product active ingredient, with results filtered for "Male" or "not specified" for sex. In the FDA Adverse Event Reporting System, "intercepted product preparation error," a medication error, was the most reported reaction overall (3855 events). The frequency of reported AEs was hot flush (19.11%), injection site pain (13.94%), death (12.52%), fatigue (7.66%), injection site mass (4.40%), prostatic specific antigen increased (3.25%), prostate cancer (2.98%), and COVID-19 (1.49%).

For Eligard 22,5 mg, during post-marketing surveillance, the following AEs were reported: Symptoms consistent with an anaphylactoid or asthmatic process have been rarely (incidence rate of about 0.002%) reported. Rash, urticaria, and photosensitivity reactions have also been reported. Localized reactions including induration and abscess have been reported at the site of injection. Symptoms consistent with fibromyalgia (e.g., joint and muscle pain, headaches, sleep disorders, gastrointestinal distress, and shortness of breath) have been reported individually and collectively.

5.4.11. Overall discussion and conclusions on clinical safety

5.4.11.1. Discussion

5.4.11.1.1. Overall assessment of available safety data

Safety data collection

The safety of Camcevi 21 mg has been evaluated in 144 patients in a Phase 3 trial FP01C-17-001. Complementarily, publications from PubMed and FAERS data have been submitted as well, and these are regarded as supportive. The PubMed search was performed on 25-August-2024 and FAERS was searched for Q1 of 2021 through Q1 of 2024.

A Pubmed literature search using the search terms leuprolide depot, 3-month (and related synonyms), and prostate cancer was performed and is considered adequate regarding the methodology, time frame, and justification for inclusion or exclusion of studies.

Patient exposure

The adverse event profile of leuprorelin products is well known. In the study FP01C-17-001, 144 patients were exposed to Camcevi 21 mg and 132 patients received the planned two doses. Their number is deemed sufficient for the evaluation of clinical safety considering all existing supportive safety data from existing similar products. All patients in the key study had prostate cancer. The study has been completed and no data beyond 6 months exists.

Safety population

The safety analysis set for this line extension, defined as any subject who received a dose of Camcevi 21 mg, comprised all subjects enrolled in main clinical Study FP01C-17-001 (N=144). In general, the population in FP01C-17-001 is suitable for the safety evaluation of Camcevi 21 mg in prostate cancer in the

EU, as the median age of the patients was 69.8 years and 88% were White. The mean duration with diagnosed prostate carcinoma was 2.37 0 ± 18.2 years. Regarding disease stage, 50.73% of subjects had prostate carcinoma stage ≥ III, while 36.1% had prostate carcinoma stage ≤ II. There were 93.8% subjects with Grade 0 and 6.25% subjects with Grade 1 in ECOG performance status. Albeit the protocol allowed patients with ECOG Performance score ≤ 2 to enter, no patients with ECOG 2 were enrolled, 9 patients (6.25%) were ECOG 1, and 135 (93.8%) ECOG 0. Thus, FP01C-17-001 differs from patients treated in everyday clinical praxis, likely to have poorer performance status and a heavier burden from comorbidities. However, this issue is not pursued further.

The comorbidities observed among the patient population — namely hypertension (53%), metabolic disorders (37%), and cardiovascular or renal diseases (3%) — are consistent with the expected demographics in this age group. As supportive material, a total of 15 published studies on 3-month depot leuprorelin forms were identified including the main studies supporting efficacy and safety of Lupron Depot 22.5 mg and Eligard 22.5 mg. Of those, 13 were primary studies, in which 2,728 prostate cancer patients received 22.5 mg of 3-month leuprolide (acetate) depot for up to 3 years, with follow-up periods extending up to 5 years. In the main study on Camcevi 42 mg, 137 subjects were enrolled and their demographics (median age 71.1 years; 89.8% White; 50.4% subjects with prostate carcinoma stage ≥ III, while 25.5% with prostate carcinoma stage ≤ II; 83.2% subjects with ECOG 0, 16.1% with ECOG 1, and 0.7% with ECOG 2) were comparable with the current study with Camcevi 21 mg.

Overall, the patient exposure for leuprorelin within the available dataset is considered acceptable for safety assessment of leuprorelin preparations. The safety population for Camcevi 21 mg is limited (144 patients), but safety data from the already marketed Camcevi 42 mg can be considered to provide supportive safety data also for this application.

Adverse events

Overall, the safety profile of Camcevi 21 mg is similar to the AEs associated with approved leuprorelin products. In FP01C-17-001, a total of 217 TEAEs were reported in 90 (62.5%) subjects. Of these, 88 treatment-emergent AEs in 53 subjects (36.8%) were considered drug-related.

The most common TEAEs were hot flush (24.3%), hypertension (11.1%), weight increased (7,6%), and injection site haemorrhage (5.6%) (by preferred term and with ≥ 5% incidence). TEAEs by preferred term without ≥ 5% limitations in the incidences were provided in the Clinical Study Report, and no new or unexpected safety findings were observed.

The most common drug-related AEs (with ≥5% frequency) were hot flush (24.31%), weight increased (7.64%), hypertension (6.25%), and injection site haemorrhage (5.56%). All drug-related TEAEs were mild (grade 1) or moderate (grade 2) in severity, 84% (74/88) and 16% (14/88), respectively.

In the initial MAA of Camcevi 42 mg, evaluable PK data from 131 patients indicated that peak concentrations are reached within 2-4 hours after injection and then the concentrations decline during the next three days. In FP01C-17-001, evaluable PK data showed that peak concentrations were reached in median 2 hours after injection, followed by a decline over the next 3 days. It was initially unclear whether the risk for post-dose AEs was associated with higher serum concentrations of leuprorelin mesilate. The Applicant provided individual time–concentration profiles for the first 3 days after dosing, annotated with the timing of AEs for

each subject. No direct relationship between serum concentrations and AE timing was observed, therefore no additional analysis of AEs in relation to the PK profile of Camcevi 21 mg is warranted at this time.

AEs of special interest, deaths, and SAEs

AEs of special interest were injection site reaction, bone and urinary pain, urinary signs and symptoms. All reported local injection site reactions were only mild in severity and were resolved by the EOS. No subjects had moderate or severe local injection site reactions. No statistically significant change was observed in bone pain assessments from Day 0 to EOS and no additional or worsened urination symptoms were caused in the subjects. However, quality of life measurements are prone to bias in open-label studies and these data are only deemed as supportive. The warning in section 4.4 in the SmPC regarding bone pain, neuropathy, haematuria, or ureteral or bladder outlet obstruction is the same as in Camcevi 42 mg, and this is endorsed although in this small study such events were infrequent.

No deaths were reported in study FP01C-17-001. Five of the published studies on 3-month depot leuprorelin forms reported deaths during the treatment period within varying amounts of follow-up time ranging from approximately 4 months to 5 years.

Ten SAEs occurred in 9 subjects (6.25%) in FP01C-17-001. All SAEs were assessed as unrelated to study drug by the investigator. One of the SAEs was a drug induced liver injury. Based on the chronology of drug administration and event onset, the pattern aligns more strongly with Pentoxifyllinum as the likely causative agent rather than Camcevi 21 mg.

One subject had acute myocardial infarction which was considered not drug related.

There were no SAEs in FP01C-13-001 that would have occurred more than once i.e. no increased frequency of a type of SAE. In the literature-based data on 3-month depot leuprorelin forms, drug-related SAEs were noted in 2 studies and included musculoskeletal chest pain and femur fracture and increase in PSA and metastases to bone. The warnings in SmPC section 4.4 regarding cardiovascular diseases and bone density and related fracture risk are unchanged compared to Camcevi 42 mg and this approach is endorsed.

Discontinuation due to adverse events

In relation to the number of patients experiencing AEs (62.5%) in FP01C-17-001, the number of patients discontinuing the study (0.7%) was low implying to relatively good tolerability. There was one subject (1/144, 0.7%) who experienced AE (stroke) that led to premature discontinuation. This event was determined to be unrelated to the Camcevi 21 mg by investigators.

Safety in special populations

The intended indication is prostate cancer, thus no between-gender differences (AEs in women), nor risk of adverse pregnancy outcomes are applicable, neither are the AEs in paediatric population.

In the current submission, the renal and hepatic impairment were defined based on the medical history terms and not to KDIGO criteria for chronic kidney disease stages 3b, 4, or 5 in case of renal impairment or Child-Pugh score B or C in case of hepatic impairment. The sample size for hepatic impairment was very limited. However, no new safety concerns emerged from these. The SmPC includes the statement "No clinical studies were performed in patients having either renal or hepatic impairment" in line with the SmPC of Camcevi 42 mg.

As the main trial had no upper limit for age, the trial had a fairly high mean age 69.8 (SD 7.93) years. In the ITT population, the incidence of TEAEs was highest in the 65–74 years group, with 71.43% of subjects (45/63) experiencing TEAEs, accounting for 105 total events. The 75–84 years group had a TEAE incidence

of 62.50% (25/40), followed by the ≥85 years group at 50.00% (2/4), and the <65 years group at 48.65% (18/37). SAEs were infrequent across all age groups. The higher AE rates observed in the older groups is expected due to the pre-existing medical conditions in the elderly population and do not indicate new safety concerns specific to Camcevi 21 mg. The very limited sample size in the ≥85-year group prevents firm conclusions for this subgroup.

Concerning body weight, the Applicant states: "Subjects with > 100 kg body weight showed decreased serum leuprorelin peak levels and overall exposure as compared to subjects < 75 kg." While this is relevant at a general level—namely, the use of a flat dose of leuprorelin irrespective of body weight—it is not considered critical in the context of this specific line extension application for Camcevi 21 mg-strength. In addition, data from this small single arm study is not expected to provide sufficient grounds to draw conclusions regarding the safety profile of Camcevi 21 mg across different weight categories. It is also expected that the frequencies of AEs increase with age, as comorbidity burden typically increase and body weight generally decrease with age. In the MAA of Camcevi 42 mg it was reported that in general, the spectrum of the most frequent AEs in aged patients did not significantly differ from what was detected in younger patients. Based on these considerations this issue do not raise major concerns.

Vital signs and laboratory findings

In literature, the fat body mass increased significantly 4.3 +/- 1.3%. In study FP01C-17-001, the body weight increase was common, 7.64%, and there was a statistically significant change from baseline, mean 0.85 kg. Although the frequency observed in this single-arm study differs from that reported in the SmPC where it is reported as uncommon, a revision of the SmPC based solely on this data is deemed not needed. This position is supported by the fact that Eligard is subject to ongoing pharmacovigilance within the EU framework, and any updates to the SmPC would be considered deems it necessary based on cumulative post-marketing surveillance data.

One patient was reported to have TEAE QT prolongation and it was assessed as drug-related. QT prolongation frequency and management is reflected in the SmPC.

No cases of anaemia were reported in FP01C-17-001 on Camcevi 21 mg, in FP01C-13-001 on Camcevi 42 and in the literature search on 3-month depot leuprorelin forms. However, in the SmPC, anaemia is reported with "common". This is based on the literature presented at the time of Camcevi 42 mg, where anaemia, including serious cases was reported as AEs of interest and with incidence common, although only two of the anaemia AEs in the literature were considered drug-related.

One subject had elevated blood glucose which was thought to be due to his pre-existing type 2 diabetes mellitus and was assessed unrelated to Camcevi by the investigator. Presence of well controlled diabetes mellitus type 2 was allowed in the exclusion criteria if only oral hypoglycaemic agents were required. In addition, blood glucose was increased in two patients (one grade 1 and one grade 3) and the increase was assessed unrelated to the study drug by the investigator. No complications of diabetes were reported like in the study FP01C-13-001 where a severe case of diabetic foot was reported. Based on the case-level data, this was confirmed and no amendments to the SmPC are deemed necessary in this context.

Postmarketing experience

Camcevi 21 mg has not been approved or marketed anywhere.

Concerning Camcevi 42 mg, the Applicant provided cumulative post-marketing data, based on global exposure of approximately 29,445 patient-treatment-years since initial authorisation. The distribution of

AEs is described and consistent with the known safety profile of GnRH agonists. No new device-related safety concerns were identified.

Concerning Eligard 22.5 mg has been marketed for decades, no new AEs in the post-marketing data are expected.

The FAERS database was searched for Q1 of 2021 through Q1 of 2024 for AEs with"leuprolide acetate" or"leuprolide mesylate". To note that FAERS database contains voluntary reports from populations of uncertain size and it is difficult to reliably estimate the frequency or establish a causal relationship to drug exposure. The most frequently ≥ 10% reported AEs were intercepted product preparation error (3855 events), hot flush (3509 events), syringe issue (3344), device leakage (2996), injection site pain (2560 events), death (2299 events), and wrong technique in product usage process (2041).

Overall, the safety results for Camcevi 21 mg in Study FP01C-17-001 are consistent with the safety profile of other leuprorelin 3-month depot formulations reported in the literature, and there are no signs of any specific product-related risks. The safety profile of leuprorelin, which has been in clinical use for many decades, is well known.

Conclusions on clinical safety

Overall, the safety results for Camcevi 21 mg in Study FP01C-17-001 are consistent with the safety profile of other leuprorelin 3-month depot formulations reported in the literature, and there are no signs of any specific product-related risks. The safety profile of leuprorelin, which has been in clinical use for many decades, is well known.

The medication errors could be less frequent with Camcevi, but class type effects, such as risk of QT prolongation, remain as safety concerns to be closely monitored. No new safety concerns emerged based on the presented literature and database sourced data. No data is available from the Eudravigilance database because Camcevi 42 mg has only been marketed in the US. This line extension is approvable from the safety point of view.

6. Risk management plan

The MAA provided vers. 2.0 of RMP (data lock point 05-02-2025 and date of final sign off 28-02-2025) in the context of this line extension application.

RMP has been updated to add Camcevi 21 mg prolonged-release suspension for injection as an additional product and to adapt the new template of EU RMP in GVP Module V (Rev. 2).

6.1. Safety specification

6.1.1. Proposed safety specification

There are no safety concerns related to the product.

No changes of the safety specification were proposed; therefore, the safety concerns remain as indicated in Table below:

Table 41: Summary of safety concerns in the proposed RMP

Summary of safety concerns	
Important identified risks	none
Important potential risks	none
Missing information	none

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

No changes are proposed to the additional pharmacovigilance activities. This is in line with Camcevi 42 mg.

6.2.1.1. Routine pharmacovigilance activities

Routine pharmacovigilance activities are sufficient. Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file are sufficient for the safety concerns.

6.2.1.2. Additional pharmacovigilance activities

No additional pharmacovigilance activities are in place for Camcevi 42 mg and consequently for Camcevi 21 mg. Routine pharmacovigilance activities are sufficient to monitor safety.

6.3. Plans for post-authorisation efficacy studies

Not applicable

6.4. Risk minimisation measures

Routine risk minimisation measures are sufficient. This is in line with Camcevi 42 mg already approved.

6.5. Overall conclusion on the Risk Management Plan

The PRAC consider that the updated risk management plan version 2.0 is acceptable.

7. Pharmacovigilance

Pharmacovigilance system

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

7.1. 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.

8. Product information

8.1. Summary of Product Characteristics (SmPC)

This is a line extension. The indication is the same as for Camcevi 42 mg.

The SmPC data presentation does not follow the current understanding of data presentation in the SmPC; however, it is mostly in line with the previous 42 mg strength and the selected reference product, Eligard 22.5 mg, and is therefore considered acceptable in the context of a hybrid application under the Article 10(3) of Directive 2001/83/EC (Guideline Reference: EMA, QRD general principles regarding the SmPC information for a generic/hybrid/biosimilar product).

8.2. User consultation

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.

9. Benefit-risk assessment

9.1. Therapeutic context

9.1.1. Disease or condition, therapeutic indication

The variation for line extension of Camcevi 21 mg was submitted under Article 10(3) of Directive 2001/83/EC using Eligard 22.5 mg as a reference product. The medicinal product is intended to be used in the same indications as the reference product and Camcevi 42 mg. Leuprorelin has been on the EU market for more than 30 years, and the reference product Eligard 22.5 mg for more than 20 years. In the EU, Camcevi 42 mg received marketing authorisation approval according to Article 10(3) of Directive 2001/83/EC ('hybrid' application) on 25 May 2022 (EU/1/22/1647/001).

The proposed indications for Camcevi 21 mg are:

- The treatment of hormone-dependent advanced prostate cancer.
- The treatment of high-risk localised and locally advanced hormone-dependent prostate cancer in combination with radiotherapy.

Camcevi 21 mg is administered as a single subcutaneous injection every three months.

In Europe, prostate cancer represents the most common cancer diagnosis in males, with 335 514 new diagnosis per year, and the third leading cause of cancer related mortality with 69 946 deaths recorded per year.[36]

Patients with locally advanced disease (clinical T3,4) or localized disease (clinical T1,2) with surrogate markers of either more advanced disease (i.e., elevated serum PSA concentrations) or more aggressive disease (i.e., poorly differentiated tumours – combined Gleason score 8 through 10) are classified as having high risk disease. For these patients, well established treatment approaches include either surgical management or external radiation therapy together with neoadjuvant and adjuvant hormone treatment. In this setting, gonadotropin-releasing hormone (GnRH) receptor agonists are used with a total treatment duration up to 3 years.

For patients with metastatic disease androgen suppression, either through surgery or with GnRH receptor agonists or GnRH receptor antagonists is the cornerstone of treatment.

In both these settings, androgen suppression aims to increase survival and for patients with advanced or metastatic disease to improve overall quality of life.

9.1.2. Available therapies and unmet medical need

This variation of MAA for line extension for a leuprorelin mesilate injectable suspension (LMIS) 25 mg, containing leuprorelin mesilate equivalent to 21 mg leuprorelin (Camcevi 21 mg), is supplied as ready-to-use drug product in contrast to the available products requiring pre-mixing prior subcutaneous injection. For a detailed description, please see section 2.1. of this document.

Camcevi 42 mg was the first ready-to-use (no pre-mixing prior to dosing) 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

[36] European Commission. Prostate cancer burden in EU-27. 2021. https://ecis.jrc.ec.europa.eu

formulations were frequently reported leading to referral procedure (refer to EMA/316598/2019). Camcevi 21 mg is a 3-month leuprorelin depot product line extension to Camcevi 42 mg and is comparable to the 3-month depot products Eligard 22.5 mg.

9.2. Main clinical studies

The study providing efficacy results for this variation is the Phase 3 study FP01C-17-001 on Camcevi 21 mg. It is a completed pivotal Phase III, uncontrolled, multicentre, open-label, single-arm, 6-month, PK, safety and PD/efficacy study conducted in 144 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, ECOG performance status ≤ 2, with a life expectancy of at least 18 months).

Subjects were scheduled to receive 2 doses of Camcevi 21 mg, spaced 3 months apart, in an unblinded fashion.

The primary objective of the clinical study FP01C-17-001 was as follows:

- To assess the efficacy and safety of Camcevi 21 mg for up to 24 weeks following 2 SC doses given 12 weeks apart in subjects with prostate cancer

The secondary objective was:

- To establish the serum PK profile of leuprolide for Camcevi 21 mg in a subset of subjects with prostate cancer

The primary endpoint of efficacy was to determine the percentage of subjects with a serum testosterone concentration suppressed to castrate levels (≤ 50 ng/dL) on Day 28 ± 1 day (week 4) following the first injection of Camcevi 21 mg, and the proportion of subjects with serum testosterone suppression (≤ 50 ng/dL) from Day 28 ± 1 day (week 4) through Day 168 ± 5 days (week 24) until the end of the study.

9.3. Favourable effects

The percentage of subjects with a serum testosterone of ≤50 ng/dL (castrate level) by Day 28 was 98.6% (141/143 subjects) in the ITT population and 98.5% (130/132 subjects) in the PP population.

The percentage of subjects with testosterone suppression from Day 28 through Day 168 was 97.9% (140/143 subjects) in the ITT population and 97.7% (129/132 subjects) in the PP population.

The percentage of subjects with a more stringent serum testosterone level ≤20 ng/dL by Day 28 was 72 % (103/143) in the ITT population and 71.2% (94/132) in the PP population. On Day 168, the percentage of subjects with suppressed serum testosterone level (≤ 20 ng/ dL) was 96.4% (135/140) in the ITT population and 96.2% (125/130) in the PP population.

The serum LH levels followed the known course of acute and transient increase after the first dose of Camcevi 21 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.

The serum PSA levels decreased along the two doses of Camcevi 21 mg until the end of the study in majority of the cases in both ITT and PP Populations (at baseline mean PSA was 34.2± 109.7 ng/mL, range 00.08-698.5 and at end of study (EOS) mean PSA was 1.2± 2.0 ng/mL, range 0.02-11.7 in the ITT population).

9.3.1. Uncertainties and limitations about favourable effects

None

9.4. Unfavourable effects

In the study FP01C-17-001, 144 patients were exposed to Camcevi 21 mg and 132 patients received the planned two doses. The AEs were reported at a rate consistent with those reported in the labelling of Eligard 22.5 mg (SmPC Eligard) and in the published literature.

The most common TEAEs (with ≥5% frequency) were hot flush (24.31%), hypertension (11.11%), weight increased (7.64%), injection site haemorrhage (5.56%). The most common drug-related AEs (with ≥5% frequency) were hot flush (24.31%), weight increased (7.64%), hypertension (6.25%), and injection site haemorrhage (5.56%). All TEAEs that were considered drug-related, were mild (grade 1) or moderate (grade 2) in severity, 84% (74/88) and 16% (14/88), respectively.

There were 10 SAEs and they occurred in 9 subjects (6.25%) in FP01C-17-001. All SAEs were assessed as unrelated to study drug. No deaths were reported in study FP01C-17-001.

Treatment was discontinued in 0.7% (1/144) of subjects. One subject experienced stroke that led to premature discontinuation. This event was determined to be unrelated to the Camcevi 21 mg by investigators.

The warnings in SmPC Section 4.4 are the same as in Camcevi 42 mg and included QT prolongation, transient testosterone flare, hyperglycaemia, reduced bone density, pituitary apoplexy, convulsions, idiopathic intracranial hypertension, severe cutaneous adverse reactions and need of close monitoring in patients with ureteral obstruction and spinal cord compression. No new ADRs were identified, the ADR Table in SmPC section 4.8 is the same as in Camcevi 42 mg and in line with the Eligard SmPC.

9.4.1. Uncertainties and limitations about unfavourable effects

The lack of comparative PD/efficacy/safety studies hampers a comprehensive assessment of the safety profile. However, this limitation is considered acceptable, given that the observed safety profile is in line with the well-known safety profile of Leuprorelin.

9.5. Effects Table

Table 42: Effects Table for Camcevi 21 mg in the treatment of hormone-sensitive prostate cancer in FP01C-17-001 (data cut-off: 19 Nov 2018).

Effect (short description)		Treatment	Control	Uncertainties/ Strength of evidence	Ref
Favourable Effects					
Serum testosterone level decrease below castrate level <50 ng/dL* % (N)	By Day 28 (± 1 day	98.6% ITT[a] (141/143) 98.5% PP[b] (130/132)	NA	**SoE:** ITT enrolled/completed 144/143; PP enrolled/completed 144/132; By Day 28 95% CI 95.0-99.8/ITT; 94.6-99.8/PP; from Day 28 through Day 168 95% CI 93.5-99.3/ITT; 93.1-99.3/PP **Unc:** -	Study FP01 C-17-001
	From Day 28 through Day 168	97.9% ITT[a] (140/143) 97.7% PP[b] (129/132)			
Serum testosterone level decrease below castrate level <20 ng/dL % (N)	On Day 28	72% ITT[a] (103/143) 71.2% PP[b] (94/132)	NA	**SoE:** On Day 28 95% CI 63.91-79.21/ITT; 62.69-78.76/PP; On Day 168 95% CI 91.86-98.83/ITT; 91.25-98.74/PP **Unc:** - A more strict castrate level has been associated with better prognosis.	
	On Day 168	96.4% ITT[a] (135/140) 96.2% PP[b] (125/130)			
Serum PSA level (clinical benefit) (ng/dL)	At baseline By Day 168	Median 8.225 ITT Median 0.5 ITT	NA	**SoE:** min, max (0.08- 698.5)/ITT at baseline; (0.02- 11.66)/ITT by Day 168 **Unc: -**	
Serum LH level (suppression) (IU/L)	At baseline By Day 168	Median 2.545 ITT Median 0.05 ITT	NA	**SoE:** min, max (0.05- 1.85))/ITT at baseline; (0.577- 18.1))/ITT by Day 168 **Unc:** -	
Unfavourable Effects					
TEAEs – total	62.50%	NA	NA		Study FP01 C-17-001
-Hot flush	24.31%	NA	NA		
-Hypertension	11.11%	NA	NA		
-Weight increased	7.64%	NA	NA		
-Injection site haemorrhage	5.56%	NA	NA		
Drug-related AEs – total	36.81%	NA	NA	The most common drug-related AEs (with >5% frequency) were hot flush (24.31%), weight increased (7.64%), hypertension (6.25%), and injection site haemorrhage (5.56%)	
SAEs – no patients, no SAEs	9/10	NA	NA		
Deaths – total %	0	NA	NA		
AEs leading to discontinuation – no patients	1	NA	NA	stroke; unrelated to Camcevi 21 mg	

Abbreviations: AE: adverse event; CI: confidence interval; EOS: end of study; LH: luteinizing hormone; NA: not applicable; PSA: prostate specific antigen; Ref: reference; Unc: uncertainties; SAE: serious adverse event; SD: standard deviation; SoE: strength of evidence; TEAE: treatment-emergent adverse event.
*primary efficacy endpoint
[a] Any subject who received at least 1 dose of Camcevi 21 mg
[b] Any subject who received 2 doses of Camcevi 21 mg, met the inclusion/exclusion criteria of the protocol, and had no major protocol violation

9.6. Benefit-risk assessment

A single-arm clinical study (FP01C-17-001) was conducted to evaluate the PK, PD, efficacy, and safety of Camcevi 21 mg, a new strength of Leuprorelin prolonged-release suspension for injection pre-filled syringe, for subcutaneous (SC) administration. The study is considered to be sufficient for establishing a PK/PD bridge to the reference medicinal product Eligard 22.5mg. The study demonstrated testosterone suppression from Day 28 through Day 168 (97.9%, 140/143 subjects) in the ITT population. Thus, the clinically relevant primary efficacy endpoint of serum testosterone concentration suppression below castrate level was met. Cross-study PK comparison (FSEE-PMX-1605) indicated similar PK characteristics following SC injections of Camcevi 21 mg and Eligard 22.5 mg.

The clinical benefit of the new leuprorelin mesilate formulation is the new simpler method of administration. Camcevi 21 mg, supplied as ready-to-use drug product, was developed to address the handling errors often reported with reference products containing leuprorelin acetate and dosed 3-monthly. Unlike these formulations that require complex pre-mixing before subcutaneous injection, Camcevi 21 mg is provided as a pre-filled syringe for a single subcutaneous injection.

The safety profile is acceptable, and well in line with the reference medicinal product Eligard 22.5mg, and other authorised leuprorelin products.

In the clinical study of Camcevi 21 mg, the efficacy endpoints (the biomarkers indicating successful ADT, i.e. testosterone, LH, and PSA) have been met. Thus, the primary efficacy endpoint of serum testosterone concentration suppression below castrate level was met and is comparable to that of other similar products.

The safety profile is comparable to the Camcevi 42 mg and the reference product and with published literature. No new safety concerns are evident.

9.7. Benefit-risk conclusions

The overall B/R of Camcevi new strength of 21 mg Leuprorelin prolonged-release suspension for injection pre-filled syringe, for subcutaneous (SC) administration, for the treatment of hormone-sensitive prostate cancer is positive.