CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205054Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	New Drug Application
Application Number(s)	205054- Original 1 (22.5 mg formulation) (b) (4)
Priority or Standard	Standard
Submit Date(s)	February 28, 2018
Received Date(s)	February 28, 2018
PDUFA Goal Date	August 28, 2018
Division/Office	Division of Oncology Product 1/ Office of Hematology and Oncology Products
Review Completion Date	August 10, 2018
Established Name	Leuprolide acetate for depot suspension
(Proposed) Trade Name	Lutrate Depot
Pharmacologic Class	Gonadotropin releasing hormone agonist
Code name	Unknown
Applicant	GP Pharma, S.A.
Formulation(s)	(b) (4) 22.5 mg depot suspension
Dosing Regimen	(b) (4) 22.5 mg intramuscular injection every 12 weeks
Applicant Proposed Indication(s)/Population(s)	Palliative treatment of advanced prostate cancer
Recommendation on Regulatory Action	Approval of 22.5 mg formulation (b) (4)
Recommended Indication(s)/Population(s) (if applicable)	Palliative treatment of advanced prostate cancer

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Janice Kim
Nonclinical Reviewer	Eias Zahalka
Nonclinical Team Leader (acting)	Tiffany Ricks
Office of Clinical Pharmacology Reviewer(s)	Salaheldin S. Hamed
Office of Clinical Pharmacology Team Leader(s)	Pengfei Song
Clinical Reviewer	V. Ellen Maher
Clinical Team Leader	V. Ellen Maher
Statistical Reviewer	Hui Zhang
Statistical Team Leader	Shenghui Tang
Associate Director for Labeling	William Pierce
Cross-Disciplinary Team Leader	V. Ellen Maher
Division Director (OCP)	Atiqur Nam Rahman
Associate Division Director (OB)	Jason Schroeder
Deputy Division Director (OHOP)	Amna Ibrahim

Additional Reviewers of Application

OPQ	Haripada Sarkar/Amit Mitra
Microbiology	Neal Sweeney
OPDP	Kevin Wright
OSI	Lauren Iacono-Connors
OSE/DMEPA	Tingting Gao
Other	Biopharmaceutics: Parnali Chatterjee

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AoC	acute-on-chronic
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GnRH	gonadotropin-releasing hormone
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSA	prostate specific antigen
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
RRT	relative retention time
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
T	testosterone
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

NDA 205054 for Lutrate Depot, [redacted] 22.5 mg for 3-month administration was resubmitted pursuant to the 505(b)(2) pathway, and the listed drug (LD) is leuprolide acetate. [redacted] The submitted NDA 205054 [redacted] original 1 for the 22.5 mg formulation [redacted] Original 1 is recommended for approval [redacted].

Lutrate Depot formulations are microsphere formulations of leuprolide acetate. Leuprolide acetate is manufactured by [redacted]. Leuprolide is trapped inside microspheres made of the biodegradable polymer [redacted] and triethyl citrate. The polymer provides a sustained release of leuprolide over a [redacted] 3-month period. [redacted] formed into a lyophilized powder that is reconstituted with an included diluent (mannitol, water, sodium hydroxide/hydrochloric acid) using the Mixject delivery device (K963583). [redacted] administered intramuscularly.

1.2. Conclusions on the Substantial Evidence of Effectiveness

GP Pharm conducted [redacted] studies using [redacted] 3 Month Formulation [redacted] enrolled patients with prostate cancer, regardless of stage. [redacted] The 3 Month Formulation (N=163) was administered every 84 days for 2 doses. [redacted] The FDA asked the Applicant to assess the percentage of patients who achieved and maintained castrate testosterone levels (< 50 ng/dL) between Days 28 and 168. The Agency's standard for approval of gonadotropin-releasing hormone (GnRH) analogues has been that the lower bound of the 95% confidence interval for the achievement and maintenance of castration should be ≥ 90%. The ability of a GnRH analogue to produce castrate testosterone levels in the majority of patients has been used as a surrogate endpoint for the approval for these agents.

[redacted]

GP Pharm further evaluated the non-castrate testosterone levels and found that at some of the time points, an interfering peak was present in the samples from patients who received the 3 Month Formulation. Multiple discussions were held with the FDA and the Applicant chose to re-analyze all samples from the study of the 3 Month Formulation. The presence of the interfering

peak and results of the original and re-analyzed testosterone levels have been carefully examined by the team and it has been determined that the results from the re-analyzed samples are acceptable for review. (b) (4)

In the current 2018 NDA submission, the percentage of patients who maintained castrate testosterone levels between Days 28 and 168 were:

(b) (4)

- 94.3% (95% CI: 89.4, 97.0) with the 3 Month Formulation.

The safety profile (b) (4) is similar to other GnRH agonists. The primary concern is tumor flare due to an initial increase in testosterone. This can result in spinal cord compression, urinary retention, and bone pain. Additional concerns include the development of metabolic syndrome with resultant hyperglycemia and cardiovascular disease. QT prolongation can occur with androgen deprivation and seizures, with and without a prior history of seizures, have been seen with GnRH analogues. The most common Grade 1-4 adverse reactions (>10%) with either formulation of Lutrate are hot flush/flushing, injection site reaction, upper respiratory infection, asthenia/fatigue/malaise, and arthralgia/arthritis. The most common (>10%) Grade 1-4 adverse reactions with Lutrate Depot 22.5 mg are hot flushes, upper respiratory infection, fatigue, diarrhea, pollakiuria, arthralgia, and injection site pain.

(b) (4)

- The team recommends approval of Lutrate Depot 22.5 mg (NDA 205054; original 1). This is based on its ability to achieve and maintain castrate testosterone levels in 94.3% of patients.

(b) (4)

1.3. Benefit-Risk Assessment

GP Pharm is seeking an indication for the palliative treatment of advanced prostate cancer. Advanced prostate cancer is a serious and life-threatening disease. Gonadotropin-releasing hormone analogues such as Lutrate Depot have been the mainstay of treatment of patients with advanced prostate cancer. Overall survival with these agents is similar to orchiectomy. The adverse event profile of GnRH analogues includes tumor flare due to an initial increase in testosterone levels and the development of metabolic syndrome. This is of particular concern because men with non-metastatic prostate cancer often receive GnRH analogues for an extended period. Lutrate Depot 22.5 mg (3 Month Formulation) has demonstrated an adequate effect on the surrogate endpoint; ability to achieve and maintain castrate testosterone levels. Lutrate Depot 22.5 mg (3 Month Formulation) has also demonstrated an acceptable safety profile similar to other GnRH agonists.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Advanced prostate cancer is a serious and life-threatening condition.	Advanced prostate cancer can result in significant morbidity and death.
Current Treatment Options	• Gonadotropin-releasing hormone analogues are the mainstay of treatment for advanced disease. Other options include docetaxel, abiraterone, enzalutamide, radium-223, and apalutamide. These agents are typically used in combination with GnRH analogues.	Gonadotropin-releasing hormone analogues are the mainstay of therapy for advanced prostate cancer. They may be used alone or in combination with other agents.
Benefit	• Overall survival with GnRH analogues is similar to orchiectomy. The approval of GnRH analogues has been based on a surrogate marker, castrate testosterone levels. The 3 Month Formulation of Lutrate Depot achieved and maintained castrate T levels in 94.3% (95% CI: 89.4, 97.0) of patients between Days 28 and 168.	Prostate cancer is responsive to testosterone. Castrate testosterone levels slow tumor growth and can result in tumor response.
Risk and Risk Management	The safety profile of Lutrate Depot 22.5 mg is similar to other GnRH agonists. The primary concern is tumor flare due to an initial increase in testosterone. Patients with impending cord compression or urinary retention should not receive GnRH agonists prior to definitive local treatment. Additional concerns include cardiovascular disease, hyperglycemia/diabetes, QT prolongation, and seizures. The most common (>10%) Grade 1-4 adverse reactions with Lutrate	The risk profile of Lutrate Depot 22.5 mg is acceptable and similar to approved GnRH agonists.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Depot 22.5 mg are hot flushes, upper respiratory infection, fatigue, diarrhea, pollakiuria, arthralgia, and injection site pain.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application, include:				
	□	Clinical outcome assessment (COA) data, such as			
			□	Patient reported outcome (PRO)	Patient questionnaire concerning bone pain, urinary pain, and urinary symptoms
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			Patient reports
	□	Patient-focused drug development or other stakeholder meeting summary reports			None
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			

	□ Other: (Please specify)	
□	Patient experience data that was not submitted in the application, but was considered in this review.	

X

Virginia Ellen Maher, M.D.
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

Advanced prostate cancer is a serious and life-threatening condition and is the most commonly diagnosed cancer in men (Surg Clin North Am 2015 95:1023). The incidence increases markedly with age. While most patients in the US present with localized disease, the 5-year life expectancy among patients with distant metastases is approximately 30%.

2.2. Analysis of Current Treatment Options

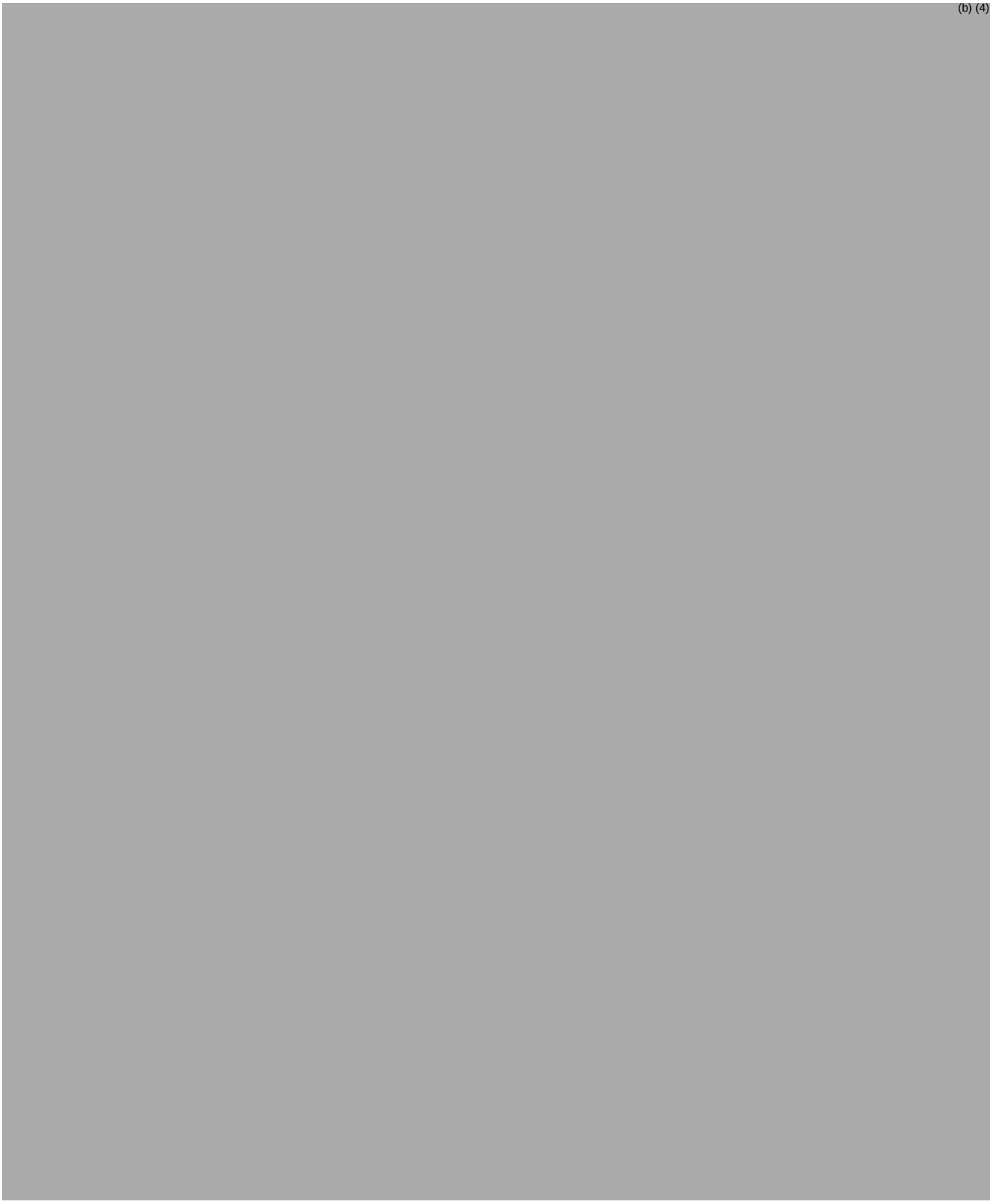
Multiple medications, including multiple generic drugs, have been approved for use in the palliative treatment of advanced prostate cancer. The approval of these drugs over several decades has led to differences in the basis of approval. The table below provides information on the trial designs of studies (other than generics) using leuprolide acetate.

Gonadotropin-releasing hormone analogues cause an initial increase and then, through down-regulation, a decrease in testosterone levels. Early in the disease, a decrease in testosterone levels results in shrinkage of castration-sensitive prostate cancers. Later in the course of the disease, prostate cancers become castration-resistant, but a portion of these tumor cells remain sensitive to testosterone. In patients with castration-resistant disease, GnRH analogues are typically continued and other agents are added to slow tumor growth.

The approval of GnRH agonists has been based on the surrogate endpoint, their ability to achieve and maintain castrate testosterone levels. An early trial comparing goserelin to orchiectomy found that they produced castrate testosterone levels in a similar proportion of patients and had similar overall survival (Urology 1995 46:220). Studies intended for the approval of GnRH agonists typically extends through 2 or 3 administrations. Achievement and maintenance of castrate T levels is typically measured: 1) at the end of the dosing interval; 2) 1-3 days after a subsequent dose or 1 to 4 hours after a subsequent dose; and 3) in the middle of the dosing interval. Measurement 1-3 days or 1 to 4 hours after a subsequent dose is done to ensure that the hypothalamic-pituitary-gonadal axis is fully desensitized. Patients who are not fully desensitized will have elevated testosterone level. The effect of this short burst of increased testosterone on tumor growth is unknown.

A key point in the design of the studies in the table below is that approval has been based on small single arm studies. Testosterone levels have been consistently measured at the end of each dosing interval, but there has been considerable variation in acute-on-chronic testing and testing during the dosing interval. Many of the trials assessed the acute-on-chronic effects in a subset of patients.

(b) (4)



3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant submitted a new drug application [redacted] (b) (4) in February 2018. Lutrate Depot has not been marketed in the U.S.

[redacted] (b) (4)

Lutrate Depot 22.5 mg was first marketed in Europe in 2015 and in countries outside of Europe in 2017. [redacted] (b) (4) reviewed through the European decentralized procedure.

3.2. Summary of Presubmission/Submission Regulatory Activity

The table below provides important information on regulatory milestones in the development of the [redacted] (b) (4) 3 Month Formulations of Lutrate Depot.

Table 2: Regulatory Milestones

Milestones	Date	Comment
[redacted] (b) (4)		
Type C Meeting	December 2005	Discussed trial design of 3 Month Formulation Agency expressed concerns about sample size and the extent/handling of missing data. Discussed CMC of [redacted] (b) (4) 3 Month Formulations
[redacted] (b) (4)		
Trial Conducted	2011-2014	3 Month Formulation
Pre-NDA Meeting	October 2012	Agency asked the Applicant to include a Kaplan-Meier estimate of the proportion of patients achieving castrate testosterone levels from Day 29-168. Agency stated that the results of the pre-specified primary analysis and the analysis using the Kaplan-Meier method should be submitted.
Original NDA	July 2014	A complete response letter citing clinical, chemistry, and inspection concerns was issued May 29, 2015
Type A Meeting	October 2015	Sponsor noted that there were interfering peaks in several testosterone analyses from the clinical trial of the 3 Month Formulation. The Agency stated that it was the sponsor's decision whether to re-analyze the samples, but that if they did

		so, they should re-analyze all samples and provide information on the re-analysis method and the long-term sample stability.
Type C Meeting	April 2016	CMC issues were discussed and the sponsor was asked to provide batch composition and formula for review as well as batch records for 3 batches.
Type C Meeting	September 2016	The manufacturing process was reviewed and the Agency stated, "We recognized you have a manufactur-ing process that is capable of producing drug product to meet your current drug product specification. The final decision on the manufacturing process and the adequacy of the manufacturing process controls will be made during the NDA review."
Resubmission	August 2017	Resubmission incomplete since a manufacturing site is not ready for inspection
Resubmission	February 2018	Current submission

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

During the initial NDA review, three clinical study sites were inspected.

- Dr. Neal Shore, Carolina Urologic Research Center
- Dr. Gary Karlin, Lawrenceville Urology
- Dr. Laurence Belkoff, Urologic Consultants at SE PA

The three sites accounted for 35% of the total patients from the US. Based on the OSI inspection summary of March 11, 2015, data from the sites appears to be reliable. Two sites were classified as no action indication while one was classified as voluntary action indication. The identified issues appeared to be isolated to that site and should not impact the overall trial.

The bioanalytical site that assayed the testosterone samples, (b) (4) was inspected during the initial review in 2014 and a Form 483 was issued. The 483 cited inadequate quality control of stability studies and inadequate information on the timing of sample processing. (b) (4) responded adequately to these findings and provided a plan for corrective action. The results of the testosterone assays were considered adequate for review.

In the current application, the Applicant submitted the results from re-analyzed testosterone samples from patients who received the 3 Month Formulation. These samples were re-analyzed

at (b) (4) and (b) (4) was again inspected. This inspection again found issues with the quality control of the stability studies. (b) (4) responded adequately to these concerns. The results from the re-analyzed testosterone samples were considered adequate for review.

During the initial 2014 review, the recommendation from the Establishment Inspection was to withhold approval. During the current submission, the facilities were again inspected and the findings were considered acceptable. See CMC review.

4.2. Product Quality

The lyophilized drug product is manufactured by forming the microspheres of leuprolide acetate with the biodegradable polymer (b) (4) triethyl citrate, methylene chloride and heptane (b) (4) microsphere (b) (4) carboxymethyl cellulose, polysorbate 80, mannitol and water for injection, (b) (4)

(b) (4)

Each vial of Lutrate Depot 22.5 mg contains (b) (4) of leuprolide acetate (b) (4)
Each vial of the 22.5 mg strength contains the following excipients: polylactic acid: 188.4 mg (235.5 mg (b) (4) triethyl citrate: 10.4 mg (13.0 mg (b) (4) mannitol: 88.4 mg (110.5 mg (b) (4) carboxymethyl cellulose: 25.0 mg (31.2 mg (b) (4) polysorbate 80: 3.8 mg (4.8 mg (b) (4) The Applicant provided data justifying the overfill (b) (4)

Each vial is supplied with a 2 mL solution of 0.8% mannitol in water (b) (4) in a prefilled syringe. When the mannitol solution is mixed with the lyophilized drug product the mixture becomes a suspension intended for intramuscular injection. The MIXJECT® sterile device allows the direct reconstitution of the (b) (4) powder using the solvent contained in the pre-filled syringe and the direct intramuscular injection of the resulting suspension into the patient. The device is fitted on the vial to pierce the stopper, and coupled to the pre-filled syringe containing the diluent, allowing the transfer of the reconstitution diluent into the vial. Once the product suspension is obtained, the device allows drawing the reconstituted product back to the syringe through the device's two-way valve. Throughout this process, the stopper is pierced only once, and the vial, device, syringe and needle stays coupled thereby ensuring the sterility of the drug product injected intramuscularly into the patient. Stability will be granted for 24 months when stored at room temperature.

(b) (4)

The product team recommends approval of Lutrate Depot 22.5 mg with a Postmarketing Requirement for in vitro testing of syringe performance for the combination product, mannitol diluent in syringe. A Postmarketing Commitment to develop an improved method for in vitro release testing has been agreed to. See CMC review for detailed information.

4.3. Clinical Microbiology

Microbiology and endotoxin testing are acceptable.

4.4. Devices and Companion Diagnostic Issues

A Postmarketing Requirement will be issued for testing, early and late in its' shelf-life, the diluent-containing syringe. This will include testing of the break loose, glide force, and dose accuracy. The Postmarketing Requirement will also include the development of a protocol for periodically testing diluent-filled syringes at the beginning and end of their shelf-life.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant submitted nonclinical pharmacokinetics, pharmacodynamics and toxicology data, which were reviewed previously on April 27, 2015 (NDA 205054 nonclinical review in DARRTS). The Applicant relied on nonclinical data from the listed drug, Lupron Depot, to support approval of Lutrate Depot. Lutrate Depot drug product contains the same active ingredient, leuprolide acetate, as the listed drug formulated in the same or lower strength. The bridge to scientifically justify reliance on nonclinical data for Lupron Depot was the combined data from the pharmacokinetic/pharmacodynamic nonclinical studies demonstrating the testosterone response following administration of Lutrate, the CMC information about the formulation of Lutrate, the toxicity study of the excipient triethyl citrate, and the available clinical data with Lutrate Depot. The Applicant also submitted a dog bridging study to the European drug product Procrin, which was used as supportive data but was not essential to bridge to Lupron Depot.

Additionally, like most nonclinical studies conducted to support an NDA, studies described in the label for Lupron Depot used the active ingredient, leuprolide acetate, rather than the Lupron Depot clinical formulation. Therefore, any differences between the Lupron Depot and Procrin formulations would not have an impact on the ability of the Applicant for Lutrate Depot to rely on those data. In the studies conducted by the Applicant of Lutrate Depot, administration of Lutrate to dogs resulted in sustained exposure and decreased testosterone over the expected period of time (b) (4) 3 months for 22.5) as would be expected for the listed drug and comparable to Procrin. Based on

the totality of the information available, the reliance on nonclinical sections of the Lupron Depot label are justified from the pharmacology/toxicology perspective.

From section 1.2 of the original nonclinical NDA review, Brief Discussion of Nonclinical Findings:

(b) (4)

(b) (4) original pharmacodynamic (PD) studies were conducted by the Applicant to assess testosterone suppression levels in dogs (a marker of activity) following a single intramuscular administration of Lutrate Depot (b) (4) 22.5 mg. The reported data showed that (b) (4) Lutrate Depot (b) (4) exhibited comparable qualitative PD profiles with regard to testosterone suppression. Castrate levels following Lutrate Depot administration were achieved between Days 7 to 21, and testosterone levels remained low until study termination. The PD endpoint was shown to be correlated with PK levels, and the PK/PD profiles were qualitatively similar across Lutrate Depot dose (b) (4) 22.5 mg).

In addition to reliance on the listed drug, the Applicant provided published safety data to further characterize the safety profile of leuprolide acetate. These safety data were considered supportive/supplemental to the nonclinical review.

The Lutrate Depot formulation contains an excipient, triethyl citrate (TEC), that was not previously characterized when administered by the intramuscular route. TEC is listed in the FDA Inactive Ingredients Search for Approved Drug Products and is contained at a maximum potency up to (b) (4) mg in an oral, delayed-action tablet. The safety profile of intramuscularly administered TEC was therefore characterized in a single- /repeat-dose (28-day) toxicology study in rats at doses which exceed that expected clinically. No adverse toxicity was reported in the TEC-treated animals. Based on this data and previous experience in approved drugs containing TEC for oral administration, this excipient was considered qualified at the specified level for intramuscular injection in Lutrate Depot.

The Lutrate Depot drug product contains the same active pharmaceutical ingredient, leuprolide acetate, as the listed drug formulated in the same or lower strength. There are no safety concerns with the excipients in the Lutrate Depot drug product. Nonclinical PK/PD studies in dogs demonstrated that the Lutrate Depot intramuscular administration resulted in exposures and testosterone responses as would be expected for the listed drug and comparable to Procrin®, a leuprolide acetate depot product approved in Europe. In addition, results from clinical trials conducted with Lutrate Depot do not indicate that there are any significant safety signals that would suggest additional nonclinical studies are needed. These combined data provide an adequate scientific bridge for reliance on the listed drug, Lupron Depot, for the

nonclinical requirements for approval as a 505(b)(2) NDA. Since FDA's findings of safety and efficacy are captured in the product labeling, no further nonclinical studies are needed to support the approval of Lutrate Depot.

The Applicant submitted an updated package insert to include the new formulation and to comply with the content and format of the Pregnancy and Lactation Labeling Rule (PLLR). See Section 11 for the changes in the package insert.

This NDA for Lutrate Depot is recommended for approval from the perspective of the pharmacology/toxicology discipline.

X X

Eias Zahalka, PhD

Acting Team Leader
Tiffany K. Ricks, PhD

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant is seeking approval for LUTRATE DEPOT (leuprolide acetate for depot suspension) [redacted] 22.5 mg given every three months for palliative treatment of advanced prostate cancer, with Lupron® Depot [redacted] 22.5 mg [redacted] NDA 020517 [redacted] as the listed drugs.

The clinical pharmacology review focuses on the acceptability of the bioanalytical method used for the reanalysis of testosterone plasma concentrations and the supportive long-term stability data from study GP/C/05/PRO – the clinical trial conducted to support the approval of the 22.5 mg formulation. Additionally, the review addresses the adequacy of bridging to the reference product from a clinical pharmacology perspective.

[redacted]

Study CP/C/05/PRO failed to meet the primary endpoint of castrate testosterone level due the presence of unidentified peaks that interfered with the quantitation of testosterone in a subset of samples. In this resubmission, the Applicant provided a modified bioanalytical method to selectively measure testosterone and the results of reanalysis of plasma samples from study GP/C/05/PRO. Additionally, the Applicant provided long-term stability data based on incurred sample reanalysis (ISR) to support the sample reanalysis plan.

The safety and efficacy data supporting the approval of the 22.5 mg formulation are obtained from an open-label, single-arm Phase 3 trial (Study GP/C/05/PRO for 22.5 mg in 163 patients). As such, no bridging to the reference product is required to support the approval from a clinical pharmacology perspective. Additionally, the PK profile of the proposed formulation was characterized in 30 patients in the study. There was no tangible accumulation observed with repeated dosing of the proposed formulation and, thus, no safety concerns.

The Office of Clinical Pharmacology has reviewed the information in support of NDA 205054 for LUTRATE DEPOT and concluded that the NDA is approvable from a clinical pharmacology perspective.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Mechanism of Action: leuprolide acetate is a GnRH agonist. Continuous administration of leuprolide in males decreases luteinizing hormone (LH), follicle stimulating hormone (FSH), dihydrotestosterone (DHT), and testosterone concentrations by desensitizing and/or down-regulating the pituitary.

Absorption: Following the first administration of the 22.5 mg formulation, plasma leuprolide concentrations increased rapidly. The peak plasma concentration was reached by 2 hours.

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

Metabolism and Elimination: No metabolism studies have been conducted for leuprolide acetate. The mean systemic clearance of leuprolide following intravenous bolus administration to healthy male volunteers was 7.6 L/h, and terminal half-life was approximately 3 hours based on a two-compartment model. No apparent accumulation was observed after the first two doses of the 22.5 mg formulation [redacted] (b) (4)

6.2.2. General Dosing and Therapeutic Individualization

Based on safety and efficacy data obtained from Study GP/C/05/PRO, the recommended dosage is 1 injection of the 22.5 mg formulation every 12 weeks. No dose adjustments based on intrinsic or extrinsic factors are listed in the approved USPI of the reference product. There are no outstanding issues from a clinical pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

PHARMACOLOGY	
Mechanism of Action	leuprolide acetate is a GnRH agonist. Continuous administration of leuprolide in males decreases LH, FSH, DHT, and testosterone concentrations by desensitizing and/or down-regulating the pituitary.
QT Prolongation	In the current submission, the Applicant did not perform a QTc prolongation evaluation. Literature suggests that androgen-deprivation therapy causes QT prolongations and it may be associated with an increased risk of cardiovascular morbidity and death. [redacted] (b) (4)

	(b) (4) The approved USPI of the reference product includes information regarding the risk of QT prolongation under the Warnings and Precautions section.
GENERAL INFORMATION	
Molecular Weight	1209.4 g/mol
Bioanalysis	Leuprolide plasma concentrations in Study GP/C/05/PRO were measured using a validated enzyme immunoassay and testosterone concentrations were measured using a liquid chromatography tandem mass spectrometry assay. Results from Study GP/C/05/PRO failed to meet the primary efficacy endpoint of sustained castrate levels of testosterone at specific timepoints. The Applicant provided evidence that interfering peaks resulted in the overestimation of testosterone concentrations in some samples. Subsequently, the Applicant provided reanalyzed study results with a validated LC/MS-MS method that selectively measured the concentrations of testosterone. Additionally, the Applicant provided long-term stability data to support the sample reanalysis plan.
Accumulation	Following two injections of the 22.5 mg formulation, there was no substantial accumulation. The profile of leuprolide concentrations following the second dose was similar to that of the first dose.
Variability	For LUTRATE DEPORT 22.5 mg, %CV of C_{max} is 38.4%; however, the %CV of AUC varies from 48.5% and 56.8% following the first two doses.
ABSORPTION	
T_{max}	T_{max} is reached after 2 hours following the first administration of the 22.5 mg.
DISTRIBUTION	
Volume of Distribution	The mean-steady state volume of distribution of leuprolide following intravenous bolus administration to healthy male volunteers was 27 L.
Plasma Protein Binding	*In vitro* binding to plasma proteins ranged from 43% to 49%.
ELIMINATION	
Mean Terminal Half-Life	The mean systemic clearance of leuprolide following intravenous bolus administration to healthy male volunteers was 7.6 L/h, and terminal half-life was approximately 3 hours based on a two-compartment model.

6.3.2. Clinical Pharmacology Questions

Are the sample reanalysis results of plasma testosterone levels acceptable?

Yes, the sample reanalysis results along with the supporting long-term stability data are acceptable.

The Applicant submitted results of (b) (4) Study GP/C/05/PRO for the 22.5 mg strength in 163 patients) (Table 3). The primary efficacy endpoint was the achievement and maintenance of castration (plasma testosterone level ≤ 0.5 ng/mL) during the study; this endpoint is a surrogate marker for demonstrating the efficacy of gonadotropin releasing hormone agonists for the palliative treatment of advanced prostate cancer. To that end, meeting the primary endpoint is based on adequate analysis of plasma testosterone concentrations.

Table 3: LUTRATE DEPOT Clinical Trials with PK Data

Study Number Location Study Design	Objective(s) of the Study	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
(b) (4)					
GP/C/05/PRO Section 5.3.5.2 Open-label	Efficacy and safety; PK analysis in a sub group of patients (30) and population PK analysis	< LEUPROLIDE DEPOT> 22.5 mg multiple dose, i.m., every 3 month	163	Patients with prostate cancer	168 days
(b) (4)					

At the time of initial submission, (b) (4) Study GP/C/05/PRO failed to meet the primary endpoint, and a Complete Response (CR) Letter was issued on 5/29/2015 (see section 3). Specifically, (b) (4) 22.5 mg) failed to achieve and maintain castrate testosterone levels in an acceptable percentage of patients. Specifically, less than 85% of the patients achieved castrate testosterone levels in (b) (4) Study GP/C/05/PRO (see section 1).

Of note, the clinical pharmacology information submitted in the original NDA to support the approval of the (b) (4) 22.5 mg formulations was found to be acceptable (see Clinical Pharmacology Review by Dr. Pengfei Song, DARRTS Reference ID: 3734222).

In this resubmission, the Applicant included the validation of a modified bioanalytical method that selectively measures testosterone and data reanalysis for testosterone in plasma samples from Study GP/C/05/PRO to support approval of the 22.5 mg formulation. (b) (4)

Bioanalysis of Testosterone (Study GP/C/05 PRO)

Detection of Peaks Interfering with Testosterone Quantification

In response to the CR letter, the Applicant attributed the failure to meet the primary efficacy endpoint in Study GP/C/05/PRO to multiple issues, one of which is the LC/MS-MS bioanalytical method used to measure testosterone levels. Specifically, upon reanalysis of testosterone chromatograms, abnormal spikes were detected in some samples.

A report from an anti-doping laboratory confirmed that these interfering peaks shared the same mass transition with testosterone, and testosterone concentrations in some plasma samples could be overestimated because of this interference. A hallmark of this interference is a distorted relative retention time (RRT), which is typically less than the RRT observed with no interference.

Based on recommendations from the anti-doping laboratory, the Applicant proposed a modified analytical method that could selectively measure testosterone concentration and exclude the interfering peaks by monitoring testosterone at a different mass transition (refer to Section 17.4.1; **Error! Reference source not found.** and **Error! Reference source not found.** for detailed description of the modified bioanalytical method). (Figure 1)

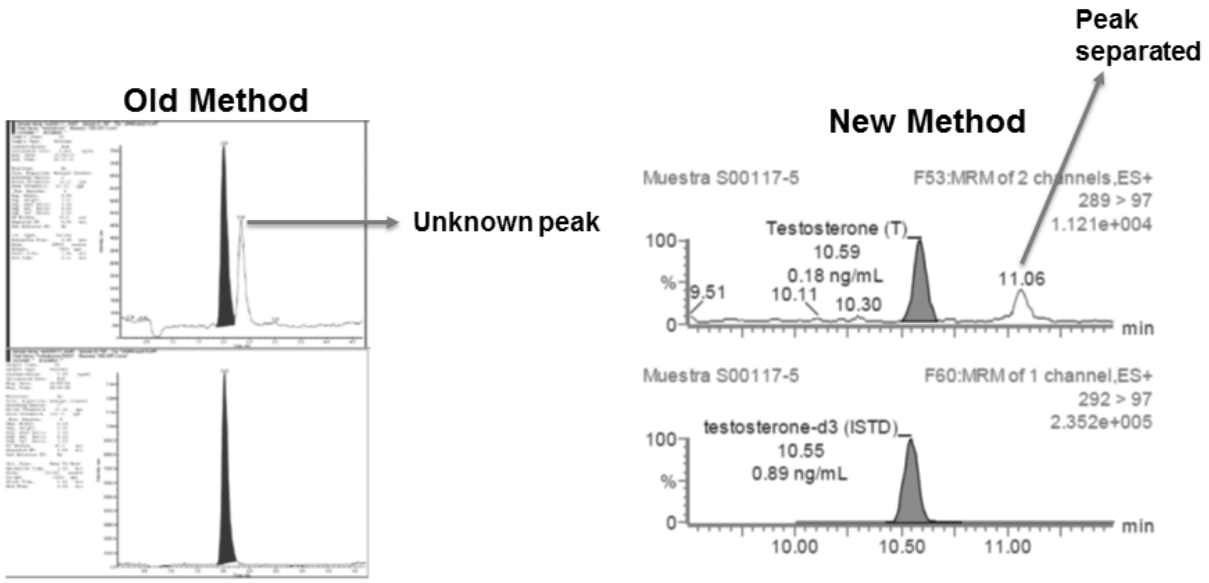


Figure 1: Interfering Peak

Presence of an interfering peak in the original (old) bioanalytical method. The modified (new) validated method can separate the interfering peak.

Sample Reanalysis (Study GP/C/05/PRO)

The sponsor selected 31 samples (based on lower RRT with the original method) for reanalysis with the modified method, 21 of which had the interfering peak and 10 were included as a control. The Agency clarified that reanalyzing a subset of the study samples might be biased and unacceptable.

The Agency recommended reanalyzing all plasma samples from study GP/C/05/PRO with the modified method and providing stability data to demonstrate that testosterone did not degrade during sample storage between the first analysis with the original method and the second reanalysis with modified method, period extending from 2013 to 2016. Based on the Agency's recommendation, testosterone was reanalyzed for all samples from Study GP/C/05/PRO with the modified LC/MS-MS method (section 17.4.1).

To demonstrate the long-term stability of testosterone in plasma samples in the period between the first and second analyses, the Applicant provided ISR for 786 samples that had a typical RRT for testosterone (i.e., no interfering peaks). The objective of the ISR is demonstrate that testosterone concentrations determined with the modified method are similar to those determined with the original method and, hence, no degradation has taken place over the storage time (Figure 2).

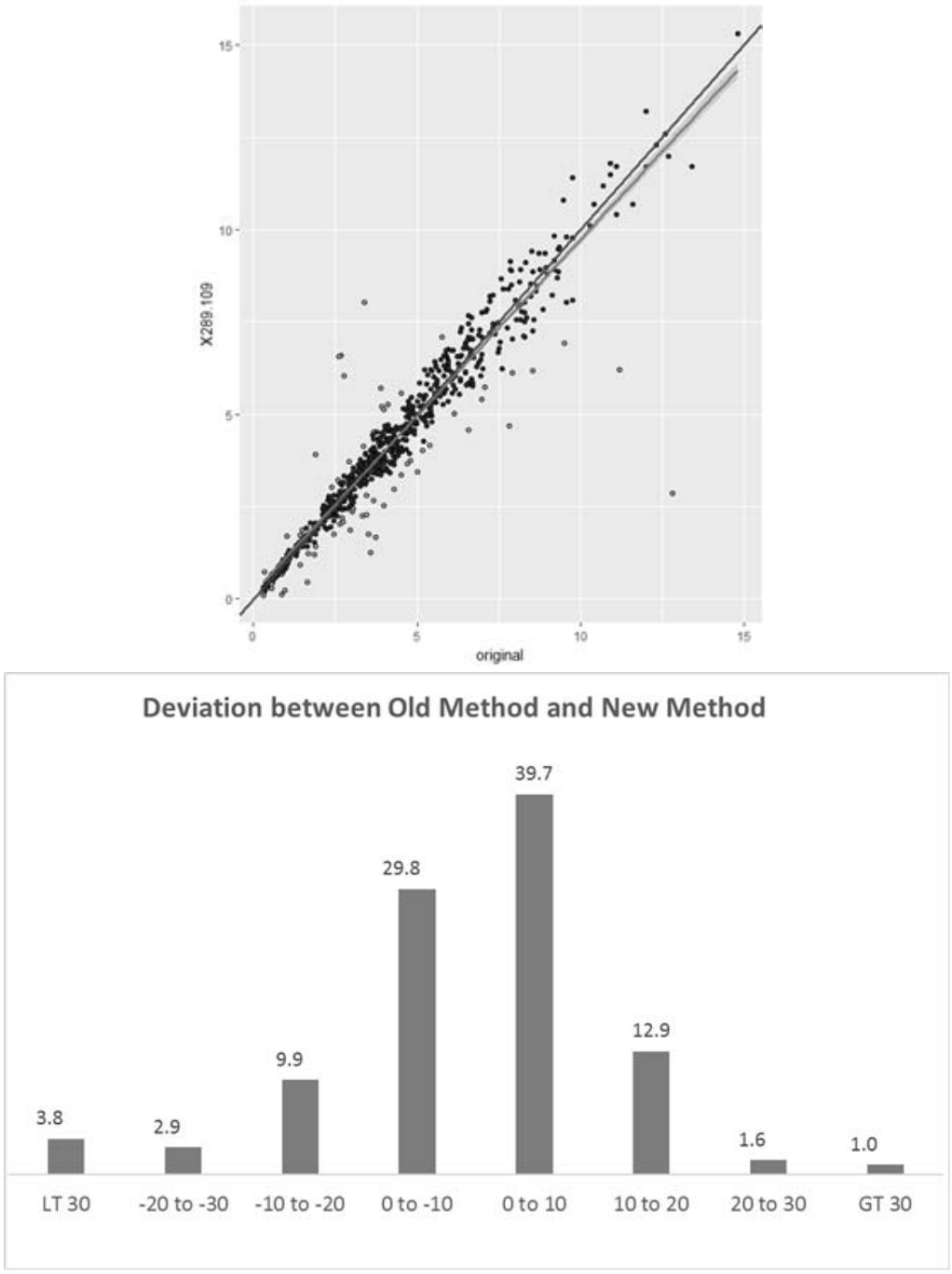


Figure 2: Results of Sample Re-analysis

ISR to demonstrate the long-term stability of testosterone in plasma samples at the time of initial analysis and after reanalysis with the modified method. Top panel: testosterone concentrations with new method are similar to the concentrations measured with the new method; samples randomly aligned around the identity line indicating no trend due to degradation. Bottom panel: >90% of samples fall within the (b) (4)% acceptance criteria for ISR.

Of note, there were two aliquots (A and B) for each plasma sample: aliquot A was sent to the bioanalytical facility and aliquot B was sent to the Applicant. The original analysis was conducted with aliquot A. The reanalysis with the modified method was conducted with aliquot A, and aliquot B was only used for samples (n=245) that did not have enough volume of aliquot A. Both aliquot A and aliquot B were stored under the same conditions (-20^{o}C). The sample traceability was found to be accurate for aliquot A and aliquot B (see section 17.4.2) and only 7 samples were found to have contradictory values for aliquot A and B. These samples were considered a failure by the Applicant in their reanalysis of efficacy results.

Based on the reanalyzed testosterone samples, Study GP/C/05/PRO met the primary endpoint. Refer to section **Error! Reference source not found.** *Study Results* for detailed statistical analysis of the reanalyzed testosterone concentrations.

Is there sufficient clinical pharmacology information to support bridging to the reference product and the approval of the proposed product?

Yes, there is sufficient clinical pharmacology information to support the approval of the proposed product.

The pivotal studies GP/C/05/PRO (b) (4) provide evidence of safety and efficacy (b) (4) Additionally, leuprolide PK was assessed in a subset of 30 patients in study GP/C/05/PRO (b) (4) As such, results (b) (4) are sufficient to support approval without the need for bridging to clinical information of Lupron®, Lucrin®, or Procrin®. The latter two are the approved Lupron products in the European Union.

Formulation Development

(b) (4)

PK Profile and Accumulation of the 22.5 mg Formulation

In study GP/C/05/PRO, the administration of the 22.5 mg formulation resulted in a rapid increase in leuprolide plasma concentrations; the peak was followed by a decline over the next several days, maintaining sustained drug levels after Day 28 until the following dose on Day 84. The leuprolide concentrations were coupled with decreased plasma testosterone concentrations below castration levels (Figure 3).

There is no tangible accumulation of leuprolide after the second dose of the 22.5 mg formulation (b) (4) As such, there is no safety concern with repeated administration of the proposed product.

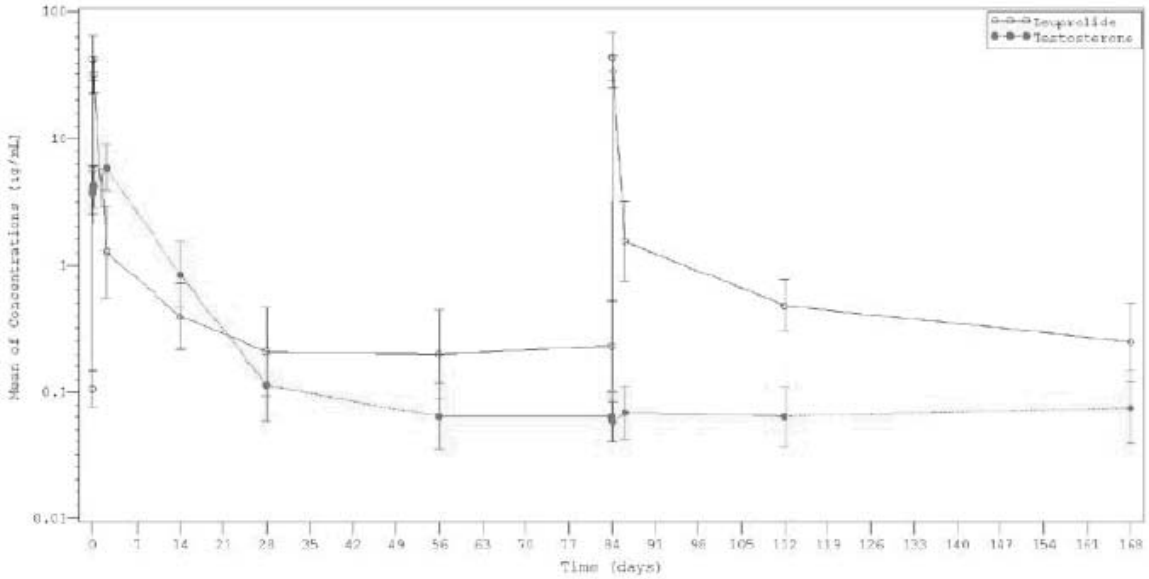


Figure 3: Plasma Leuprolide and Testosterone Concentrations

X X

Salaheldin S. Hamed, Ph.D. Pengfei Song, Ph.D.

Primary Reviewer Team Leader

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Phase	Title	# Patients	Study Design
[redacted]			(b) (4)
Phase 3	**GP/C/05/PRO** Efficacy and Safety of a New Leuprolide Acetate 22.5 mg Depot Formulation in the Treatment of Prostate Cancer	163	Open-label, single-arm study, with 2 doses of Lutrate Depot 22.5 mg administered intramuscularly every 84 days

7.2. Review Strategy

Based on the study design and reported results (b) (4), the reviewers examined the study protocols, statistical analysis plans, submitted datasets and study reports. The focus was on evaluating whether castration was achieved and maintained (b) (4) The reviewers conducted independent analyses based on the reported testosterone values from the central laboratory. Safety evaluation focused on signals that had been seen with other GnRH analogues and on any signals that appeared specific to Lutrate Depot.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. (b) (4) CRO-GP-C-05-PRO (3 Month)

(b) (4)

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Study CRO-GP-C-05-PRO (3 Month Formulation)

Design of Study

This was an open-label, single-arm trial to study the effect of Lutrate Depot 22.5 mg every 84 days on testosterone levels.

Key Eligibility Criteria

1. Histologically proven carcinoma of the prostate
2. Might benefit from medical androgen deprivation therapy
3. Testosterone ≥ 150 ng/dL by local laboratory
4. No androgen ablation within 12 mos or lasting > 6 mos; No use of androgen receptor inhibitors within 3 mos; No prior systemic prostate cancer treatment; No radiation therapy or surgery to prostate within 2 wks; No 5-α-reductase inhibitors within 3 mos; No over-the-counter therapies with an estrogenic or anti-androgenic effect within 3 mos
5. No evidence of spinal cord compression, severe urinary obstruction, severe pain from bone metastases, or brain metastases
6. Life expectancy at least 1 year; ECOG Performance Status score of 0-2
7. Creatinine ≤1.6 times the upper limit of normal (ULN); Grade 0-1 AST, ALT, and bilirubin
8. No uncontrolled diabetes; No uncontrolled heart failure; No myocardial infarction, coronary vascular procedure, or significant symptomatic cardiovascular disease within 6 mos of entry; No uncontrolled hypertension within 3 mos;
9. No venous thrombosis within 6 mos; No full dose anticoagulants

Treatment
Lutrate Depot 22.5 mg intramuscularly every 84 days x 2

Concomitant Medications
Androgen receptor inhibitors and other GnRH analogues were prohibited. No anticoagulants that would affect PT/PTT. Anti-platelet agents were allowed. No mention of radiation therapy.

Safety Monitoring
Safety laboratories and EKGs were obtained at baseline and on Days 28, 84, 112 and at the end of treatment visit on Day 168.

The injection site was assessed immediately after each injection. The site of the 1st injection on Day 0 was also assessed at 15 and 30 minutes and at 1 and 3 hours post-injection. The site of the 2nd injection on Day 28 was assessed at 15 and 30 minutes and at 1-hour post-injection. Patients were also asked to record any local reactions at the injection site in a patient diary.

Adverse events were collected throughout the treatment period. Investigators were to specifically ask patients about the development of hot flushes on Days 2, 14, 28, 56, 84,86, 112, and 168.

Efficacy Assessments
Testosterone, FSH and LH were obtained on the following schedule.

- Pre-dose and 1 and 4 hours after the 1st dose on Day 0; Days 2, 14, 28, and 56.
- Pre-dose and 1 and 4 hours after the 2nd dose on Day 84; Days 86, 112, and 168.

Samples were assayed at a central laboratory, (b) (4) Testosterone was assessed using gas chromatography-mass spectroscopy with a lower limit of quantitation of 10 ng/dL.

Prostate-specific antigen was assessed, by (b) (4) at baseline and Days 14, 28, 56, 84, 112, and 168.

Bone pain, urinary pain, and urinary symptoms were assessed at baseline and on Days 2, 14, 28, 56, 84, 86, 112, and 168. Patient were asked to rate these 3 items on a 10-point scale where 1 was no and 10 was the worst pain/symptoms possible.

Study Endpoints

Statistical Analysis Plan (SAP)

Efficacy Measures
Per the final SAP, the primary efficacy endpoint was the proportion of successful patients over the total number of evaluable patients (i.e. $N_{successes}/N_{evaluable\ patients}$). For each patient, success was defined as castration (castrate testosterone defined as ≤ 50 ng/dL) at Days 28, 84, and 168. These are referred to as key time points. Patients with missing data at key time points were considered non-castrate at these time points. However, if the reason that the data was missing was unrelated to study drug, the patient could be considered castrate at that time point.

In the current 2018 NDA submission, the Applicant used data from re-analyzed testosterone levels and analyzed the primary efficacy endpoint using the Kaplan-Meier method. Success was defined as achievement and maintenance of castration: Patients who achieve testosterone concentration ≤ 50 ng/dL at Day 28 and maintained castrate testosterone values until Day 168. A patient was considered have had an event if: 1) Testosterone concentration above 50 ng/dL from Day 28 onwards, 2) Different testosterone results between Aliquots A and B from Day 28 onwards, 3) Insufficient sample for re-analysis from Day 28 onwards, and 4) Missing data due to an adverse event related to study drug.

In the current primary analysis, patients with a castrate testosterone level who withdrew were censored at the last time point with an available testosterone level. Patients who did not have a testosterone level drawn at a given time point and had a prior castrate value were considered castrate at the missing time point. Patients with a missing (not drawn) value and a non-castrate value after the missing time point are considered to have had an event at the missing time

point. Patients with a castrate testosterone level and two subsequent consecutive missing (not drawn) values are censored at the last time point with a castrate testosterone level. Due to concerns about the use of re-analyzed samples, time points at which a sample was not available for re-analysis (i.e., the sample had been drawn, but insufficient sample remained for re-analysis) were considered non-castrate. Time points at which results were available from both Aliquots A and B were considered non-castrate if the result from either aliquot was non-castrate.

Analysis Sets
Per the final SAP, the primary efficacy analysis population included patients who received at least one dose of study drug and had data at one or more key time points (Days 28, 84, 168). The FDA analysis included patients who received one dose of study drug and had a testosterone level at Day 28. Patients with missing data at Day 28 were considered non-castrate at that time point.

Sample Size Considerations
The null hypothesis was that the proportion of successful patients was 93%. With a sample size of 144 patients, the study would have 80% power to demonstrate that the proportion of successful patients exceeded 93% at a two-sided 5% significance level if the underlying proportion of successful patients was 98% based on an exact test. With a maximum dropout rate of 10%, the study planned to enroll 160 patients.

Secondary endpoints included: 1) testosterone concentration and pharmacodynamic parameters; 2) LH, FSH, and PSA levels; 3) performance status; and 4) bone pain, urinary pain, and urinary symptoms.

Protocol Amendments
None

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant has stated that studies (b) (4) 3 Month Formulations were conducted in accordance with the general principles of the International Conference on Harmonization E6. The quality of this submission was acceptable. However, the quality of the data presentation was not consistent with that of other Agency submissions.

Financial Disclosure

A FDA Form 3454 signed by Antonio Duena, Chairman of GP Pharm, S.A., was submitted certifying that the Investigators involved in the studies (b) (4) 3 Month Formulations had no financial interests to disclose.

Patient Disposition

Patients who discontinued prior to each of the dose and the reasons for discontinuation are included in the table below.

(b) (4)

One dose of the 3 Month Formulation was administered to 163 patients and two doses to 157 patients with 151 patients completing follow up. Causes of discontinuation include use of radiation therapy (2), initiation of bicalutamide (1), and initiation of triptorelin (1).

Table 4: Patient Disposition

	(b) (4)	3 Month Formulation
Enrolled		163
Received 1st Dose		163
Protocol Violation		1
Patient/Investigator Decision		4
Other		1
Received 2nd Dose		157
Protocol Violation		2
Patient/Investigator Decision		3
Other		1
Received 3rd Dose		NA
Patient/Investigator Decision		
Adverse Event		
Received 4th Dose		
Received 5th Dose		
Patient/Investigator Decision		
Received 6th Dose		
Patient Death		
Adverse Event.		

Protocol Violations/Deviations

The protocol deviation dataset for the (b) (4) Review of other datasets 1 patient (b) (6) with a low baseline testosterone, two who received brachytherapy (b) (6) and two who underwent

transurethral resection of the prostate (TURP) (b) (6). While brachytherapy is not thought to affect testosterone levels, most studies have obtained testosterone levels 3 months after treatment. Therefore, the acute effect of brachytherapy on testosterone is unknown (Int J Radiation Oncology Biol Phys 2012 82:e33).

The table below provides information on protocol violations among patients who received the 3 Month Formulation. These were reported in 131/163 (80%) patients. Two patients (b) (6) previously received a GnRH analogue. Review of the protocol deviation and other datasets found that in addition to those whose discontinuations are included in the Patient Disposition above, 3 patients (b) (6) who received external beam radiation. The Applicant provided a reference that stated that most patients have a decrease in testosterone with external beam radiation, but that the median time to decrease was 6.4 months (J Sex Med 2017 14:876). Pickles et al found that testosterone levels 2 months after external beam radiation were approximately 95% of baseline (J Urol 2002 167:2448).

Table 5: Protocol Deviations-3 Month Formulation

Protocol Violation	**3 Month Formulation N = 163**
Any	131
Eligibility Criteria	32
Informed Consent	10
Study Medication	1
Diary Not Completed/Returned	6
Prohibited Medication	7
Assessment Not Performed Failure to Adhere to Visit Schedule	120
Other	7

(b) (4) required that patients have a testosterone level ≥ 150 ng/dL by local laboratory. Most trials require a higher baseline level. (b) (4) two patients (b) (6) were ineligible due to low baseline local laboratory testosterone levels and a level was not drawn in patient (b) (6). Central laboratory testosterone levels from these 3 patients were all ≥ 150 ng/dL. However, four patients (b) (6) had central laboratory testosterone levels below the required 150 ng/dL. None of these four patients had a testosterone level < 150 ng/dL by local laboratory.

Among the patients who received the 3 Month Formulation, 150/163 had a local laboratory testosterone level and none were < 150 ng/dL. Of the 13 patients with missing values, none had a central laboratory testosterone level < 150 ng/dL. Therefore, none of the patients were ineligible, but the substantial number of patients with missing baseline levels by local laboratory was of concern.

By central laboratory testing, five to seven patients who received the 3 Month Formulation had a baseline T level < 150 ng/dL. None of these patients had a local laboratory testosterone level < 150 ng/dL. Local laboratory, original central laboratory, and re-analyzed central laboratory results for these patients are shown in the table below. While central testing should be more accurate, there was substantial variation between the original and re-analyzed results, calling into question the statement that the central laboratory results are more accurate. Patient (b) (6) had received Lupron prior to study entry.

Table 6: Low Baseline Testosterone Levels-3 Month Formulation

Testosterone Levels (ng/dL)			
	Local Laboratory	Central Laboratories	
		Original	Re-analyzed
(b) (6)	205	163	143
	151	142	174
	171	990	148
	178	118	127
	154	131	137
	174	63	65
	183	137	147

Table of Demographic Characteristics

The table below provides information on patient demographics from all treated patients and all patients included in the primary analyses of the two trials. Since the primary analyses assess testosterone levels after Day 28, the number of patients in the primary analyses is lower than the number treated. There were a substantial number of African-American patients and a substantial number of US patients were enrolled on these trials.

Since limited data was available concerning baseline disease characteristics, these are included with the demographics. (b) (4) For the 3 Month Formulation, median baseline PSA, values less than the LLOQ were considered to be at the LLOQ and values > 1080 or greater than the upper limit of quantitation were considered to be 1080 ng/mL.

Table 7: Patient Demographics and Baseline Disease Characteristics

	(b) (4)	3 Month Formulation	
		All Treated[1] N = 163 (%)	Primary Analysis Population[1] N = 162 (%)
Median Age (range)		72 years (47-91)	72 years (47-91)
Race			
White		101 (62)	101 (62)
African-American		49 (30)	49 (30)
Other		13 (8)	12 (8)
Performance Status			
0		137 (84)	136 (84)
1		22 (13)	22 (14)
2		4 (2)	4 (2)
Region of Enrollment			
United States		163 (100)	162 (100)
Eastern Europe		0	0
Western Europe/Australia		0	0
Median BMI (kg/m^2) (range)		28.2 (16.9-71.6)	28.3 (16.9-71.6)
Median Baseline Testosterone (ng/dL) (range)		365 (151-1136)	363 (151-1136)
Median Baseline PSA (ng/mL) (range)		6.41 (0.36-1080.0)	6.24 (0.36-1080.0)
Metastatic Disease at Baseline		18 (11)	18

Abbreviations: BMI-body mass index; [1]For some values, data was not available for all patients; [2]One testosterone level reported as 635 ng/mL was considered to be 635 ng/dL.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Limited information was captured concerning the baseline disease characteristics. See information in table above.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Injections were administered at the clinical sites and could be fully assessed. See Patient Disposition above concerning the number of patients who received each dose of study drug.

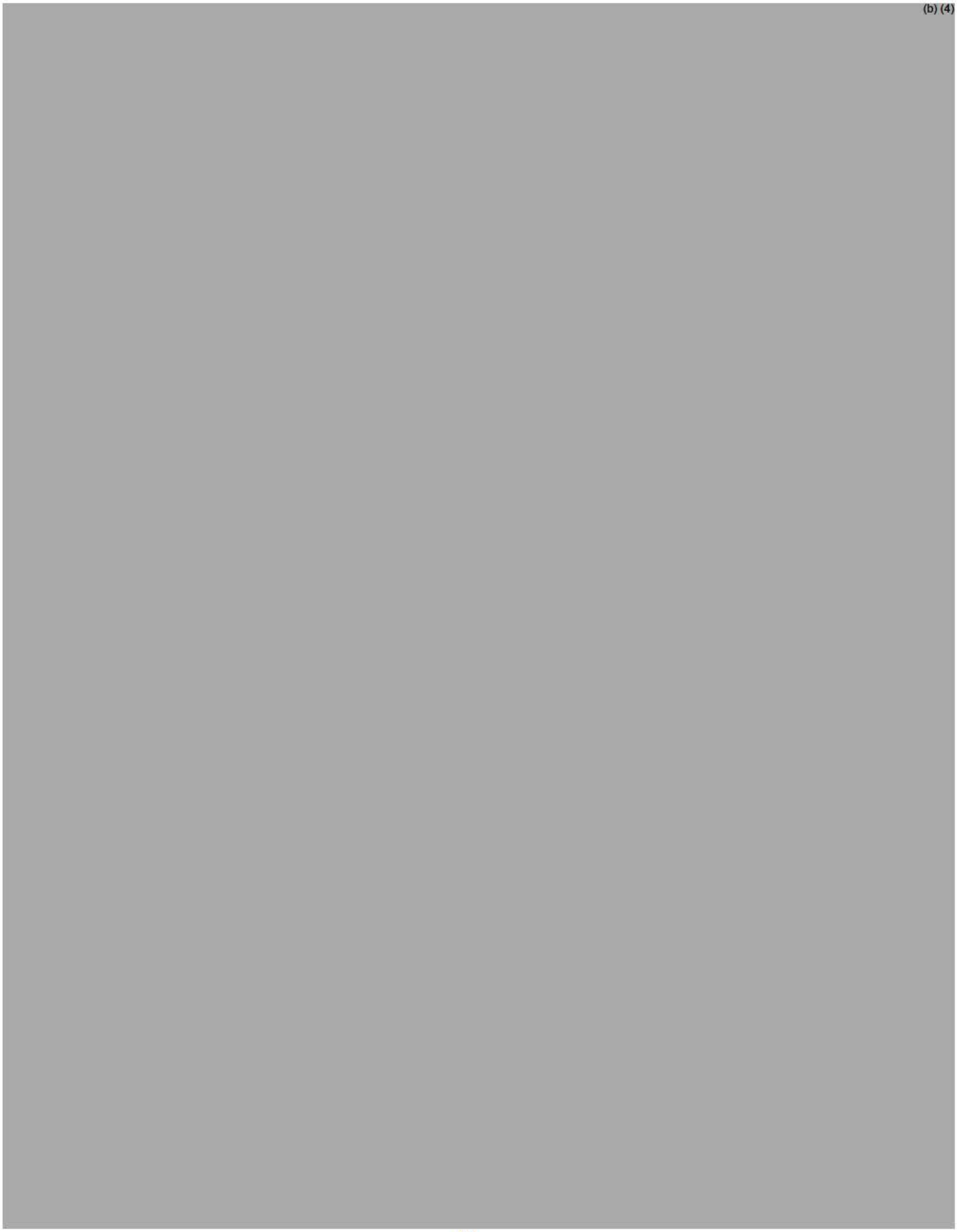
Concomitant medications that may lower the testosterone level or are purported to have activity in prostate cancer were examined. (b) (4) mong the 163 patients who received the 3 Month Formulation, patient (b) (6) received triptorelin after the 2nd dose, but prior to completion of follow up. This patient was censored in the primary analysis. Patient (b) (6) received saw palmetto.

Efficacy Results – Primary Endpoint

Both trials evaluated the percentage of patients who achieved and maintained castrate testosterone levels during the treatment period. The tables below provide information on the current analyses of the primary endpoint by the Agency and the Applicant. A discussion of the differences between these results, including the re-analysis of the testosterone samples from patients receiving the 3 Month Formulation, and the Applicant's rationale for the acceptability of these results follows.

(b) (4)

(b) (4)



3 Month Formulation

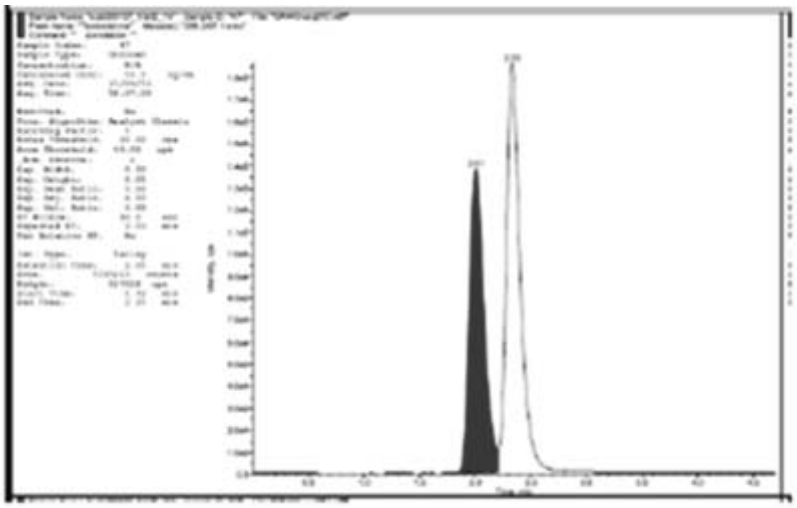
Based on the original analysis of the testosterone samples

The Applicant's original analysis, as pre-specified in the statistical plan, involved only testosterone levels on Days 28, 84, and 168. The number of patients with castrate or missing levels at these times points was divided by the number of evaluable patients and the percentage calculated. This pre-specified method of analysis, using the original testosterone results, found that 98.1% (95% CI: 94.7, 99.6) of patients achieved castration. The Agency's Kaplan-Meier analysis, which is a preferred method, using the original testosterone results, found that 83.9% (95% CI: 77.3, 88.8) achieved and maintained castrate testosterone levels between Days 28 and 168. Based on the inability of these results to meet the efficacy standard set by the FDA, the Applicant was issued a complete response letter.

Interference with Testosterone Measurement and Reanalysis

Following the original NDA submission and receipt of the complete response letter, the Applicant investigated the curves that were used to obtain the testosterone levels and noted an interfering peak in some assays. See figure below for a representative example. Interfering peaks were noted in 25 patients at 31 time points. Most patients had an interfering peak at a single time point, but several had interfering peaks at 1-2 time points. The substance causing this peak is unknown and it is difficult to understand how it could be seen intermittently.

Figure 4: Interfering Testosterone Peak



After noting the presence of this interfering peak, the Applicant had all the samples re-analyzed using a different method. Two of the issues involved with the re-analysis were the prolonged storage of the samples and the availability of these samples. This study was conducted from 2011 to 2013. These samples had been stored for several years and degradation of the testosterone was a concern. However, an overall comparison of the results of original and re-analyzed samples found that 703 re-analyzed samples had a higher reported testosterone level than the original value and 586 a lower value. More than 90% of re-analyzed samples had a testosterone level that was within 20% of the original result. This suggests adequate storage of the samples. The data were, therefore, considered adequate for analysis.

During the study, samples were split into Aliquots A and B. (b) (4) ran the original testosterone assay on Aliquot A and stored the remainder of the sample. Aliquot B was shipped to the Applicant. Both aliquots were stored at -20^0 C. For the re-analysis, Aliquot A was used in most instances. Aliquot B was used when insufficient material was available from Aliquot A and Aliquot B was used. An overall comparison of the results of analyses of Aliquots A and B found that among 703 samples in which the re-analyzed value was higher, 88/703 (12.5%) were Aliquot B. Among the 586 samples in which the re-analyzed value was lower, 86/586 (14.7%) were Aliquot B. Again, the data is adequate for analysis.

Note in this scenario, if results were available from both Aliquots A and B for a given time point and either value was non-castrate, the patient was considered non-castrate at that time point.

Based on re-analyzed testosterone samples

With the results of the re-analyzed samples, the Applicant and the Agency generated the following results for the primary analysis using the Kaplan-Meier method. Because this analysis involved re-analyzed samples, there were time points at which no sample was available. In the primary analysis, patients were considered non-castrate if no sample was available for re-analysis. A sensitivity analysis was conducted to address this issue (see below). A small number of patients had results from both Aliquot A and B at a given time point. If the result from either of these aliquots was > 50 ng/dL, the patient was considered non-castrate at that time point.

Table 9: Primary Analysis: 3 Month Formulation

	Agency Analysis N = 162	**Applicant Analysis N = 161**
Percentage with Castrate Testosterone Levels* Days 28-168 (95% CI)	94.3% (89.4, 97.0)	95.0% (90.1, 97.4)

*Lower limit of quantitation is 10 ng/dL.

There were 163 treated patients. The Applicant did not include patients (b) (6) in their analysis stating that patient (b) (6) was excluded due to a lack of response to queries from the site and patient (b) (6) withdrew at Day 3. Patient (b) (6) had available T levels until Day 56 (castrate after Day 28) and but withdrew on Day 84 due to a protocol violation, initiation of radiation therapy after Day 28. Patient (b) (6) was included in the FDA analysis and censored at Day 28. Patient (b) (6) was not included in the FDA analysis.

The Agency considers nine patients to have had non-castrate time points between Days 28 and 168. The table and the bullets below provide information of these non-castrate time points.

- Day 28:
  - Patient (b) (6) had a non-castrate T level.
  - Patient (b) (6) did not have a sample from Day 28 and his Day 14 sample was non-castrate.

- Mid-cycle: Day 56
  - Patients (b) (6) had non-castrate levels at Day 56.
  - Patient (b) (6) had an insufficient sample for re-analysis at Day 56.
  - Patient (b) (6) had a non-castrate level at Day 128; this was the final visit sample.

- End of Dosing Interval: Day 84 pre-dose, Day 168
  - Patient (b) (6) had a non-castrate level at Day 168.
  - Patient (b) (6) had an insufficient sample for re-analysis at Day 84.
  - Patient (b) (6) was withdrawn from the study and was censored at Day 56.

- Acute-on-Chronic: Day 84 1 and 4 hrs post-dose, Day 86
  - Patients (b) (6) had non-castrate levels.

- Patients (b) (6) had insufficient samples for re-analysis; note that Patient (b) (6) had a non-castrate level at Day 168.

Based on the both the re-analysis and original analysis of the testosterone samples.

Comparison of re-analyzed/original testosterone levels with interfering peaks found that interfering peaks occurred at 31 time points. These were not clustered by patient number or time point. There were no concomitant medications that could explain the interfering peaks.

The table below provides all non-castrate testosterone levels on re-analysis. The 9 time points with an interfering peak in the original analysis and a re-analyzed sample with a non-castrate T level are shaded in grey. Note that this table does not show the 22 time points at which the re-analyzed sample was castrate. At seven of the nine time points, the re-analyzed sample was non-castrate. The remaining two were considered non-castrate due to an inadequate sample for re-analysis. Importantly, among the seven, four had a marked difference in results from Aliquots A and B and all were considered non-castrate. At each of these time points, the original testosterone level was non-castrate. The difference seen between Aliquots A and B is not consistent with an interfering peak that is resolved with an improved testing method. The non-castrate value was used in the primary analysis.

Table 10: Non-castrate Testosterone Level on Re-analysis

Patient	**Time Point**	**Original T Level** (ng/dL)	**Re-analyzed T Level** (ng/dL)
(b) (6)	Day 84 1 hour	< 10	Insufficient sample
	Day 168	23.5	836 Aliquot A < 10 Aliquot B
	Day 128	279	291 Aliquot A 28.5 Aliquot B
	Day 28	Missing	Missing
	Day 84 4 hours	111	Insufficient sample
	Day 84 pre-dose	< 10	Insufficient sample
	Day 28	33.4	257
	Day 56	91.6	91.7 Aliquot A 28.8 Aliquot B
	Day 56	185	121
	Day 84 1 hour	149	187 Aliquot A 36.2 Aliquot B
	Day 84 4 hour	78.3	90.3
	Day 168	< 10	43.8 Aliquot A 50.6 Aliquot B
	Day 56	52.7	Insufficient Sample
	Day 86	71.1	71.1 Aliquot A 23.3 Aliquot B

* First non-castrate value

Since patients with an insufficient sample for re-analysis were considered non-castrate in the primary analysis, a sensitivity analysis was conducted to address this issue.

- Patient (b) (6): In the primary analysis, he was non-castrate at Day 84 due to an insufficient sample for re-analysis. In this sensitivity analysis, he was considered castrate at Day 84. However, he was non-castrate at Day 168 based on re-analyzed testosterone level.
- Patient (b) (6) In the primary analysis, he was non-castrate at Day 84 due to an insufficient sample for re-analysis. In this sensitivity analysis, he was non-castrate at Day 84 since the original testosterone level was > 50 ng/dL.
- Patient (b) (6): In the primary analysis, he was non-castrate at Day 84 due to an insufficient sample. In this sensitivity analysis, he was considered castrate at all time points.
- Patient (b) (6): In the primary analysis, he was non-castrate at Day 56 due to an insufficient sample. In this sensitivity analysis, he was non-castrate at Day 56 since the original testosterone level was > 50 ng/dL.

In this sensitivity analysis, castrate levels of serum testosterone were achieved and maintained from Day 28 to 168 in 94.9% (95% CI: 90.1, 97.4) of patients. The results are consistent with the Agency's primary findings.

A second sensitivity analysis censored patients 154 and 190 prior to administration of radiation therapy. The result of this analysis was that 94.3% of patients achieved and maintained castrate testosterone levels from Days 28-168.

Data Quality and Integrity

The organization and presentation of data in this submission in not consistent with other Agency submissions. However, the data could be analyzed. More importantly, inspections of both clinical sites and the testosterone analysis facility were considered adequate.

Efficacy Results – Secondary and other relevant endpoints

Both studies included LH, FSH, and PSA as secondary endpoints. Luteinizing hormone and FSH levels were not analyzed. Findings from evaluation of these laboratories does not add to the results of the analyses of testosterone. Further, there are no accepted normal range for LH and FSH, no agreed upon values for elevation following administration of a GnRH agonist, and no agreed upon values for suppression following down regulation.

The study of the 3 Month Formulation also included an analysis of ECOG performance status and testosterone levels over time. Testosterone levels over time were evaluated for both trials.

Testosterone Levels

The following tables shows the mean and median testosterone levels over time. As with other GnRH agonists, there is an initial surge followed by the development of castrate levels. Note that mean values are insensitive to the number of non-castrate testosterone levels. In this analysis, values of 0 or < LLOQ were assigned the LLOQ.

Table 12: Mean and Median Re-analyzed Testosterone Level Over Time-3 Month Formulation

Visit	N	Mean (SD)	Median
Baseline	161	400.4 (167.4) ng/dL	369.0 ng/dL
Baseline 1H	160	430.5 (180.5)	388.5
Baseline 4H	159	437.5 (191.9)	402.0
Day 2	161	617.3 (281.2)	580.0
Day 14	162	101.0 (064.6)	84.3
Day 28	161	17.1 (20.2)	13.6
Day 56	161	12.5 (11.3)	BLQ
Day 84	159	11.4 (03.6)	BLQ

Visit	N	Mean (SD)	Median
Day 84 1H	152	12.0 (14.5)	BLQ
Day 84 4H	150	11.5 (7.4)	BLQ
Day 86	156	11.9 (6.0)	BLQ
Day 112	156	11.7 (4.1)	BLQ
Day 168	152	19.0 (70.6)	BLQ

- The LLOQ was 10 ng/dL.
- Patient 46 had an early termination visit at Day 128. This T value was included in the Day 168 visit.

Prostate Specific Antigen

Increases in PSA during the initial 28 days and changes in PSA in patients with non-castrate testosterone levels were examined. (b) (4) Among the 163 patients receiving the 3 Month Formulation, 161 had a baseline and Day 28 value. Ten patients had an increase in PSA from Day 0 to 28. These increases ranged from 0.03 to 17.6 ng/mL.

Prostate specific antigen was also examined (b) (4) Among 23 patients with available PSA levels, three had an elevation in PSA following the non-castrate testosterone level. These increases ranged from 0.07 to 6.3 ng/mL. Among the 6 patients with non-castrate testosterone levels who received the 3 Month Formulation, all had a decrease in PSA at time points after the non-castrate level. While it is encouraging that few or no patients had an increase in PSA, changes in PSA do not always reflect changes in the tumor.

The table below provides information of PSA levels over time. The low baseline PSAs reflects the large number of patients with localized disease. Both formulations resulted in a marked decrease in PSA over the treatment period.

(b) (4)

Table 14: Mean and Median PSA Level Over Time-3 Month Formulation

Visit	N	Mean (SD)	Median
Baseline	162	44.75 (165.37) ng/mL	6.24 ng/mL
Day 14	156	45.16 (166.73)	5.21
Day 28	161	17.42 (92.54)	2.62
Day 56	162	6.24 (27.98)	0.69
Day 84	159	5.27 (31.46)	0.47
Day 112	152	6.26 (42.31)	BLQ
Day 168	152	4.75 (29.70)	BLQ

- Values reported as < the LLOQ were assigned the LLOQ, 0.36 ng/mL.
- Values reported as > 1080 or > the upper limit of quantitation were assigned 1080 ng/mL.
- Patient 46 had an early termination visit at Day 128. This PSA value was included in Day 168 visit.

Durability of Response

The effect of GnRH analogues, as determined by a decrease in testosterone, can persist after discontinuation. The duration of low testosterone levels following discontinuation is largely dependent on patient age (J Urol 2008 180:1432). Early in the disease course, patients are sometimes given “drug holidays” with resumed dosing triggered by changes in PSA. The effect of “drug holidays” on patient outcome continues to be debated (NEJM 2013 368:1314). In most patients, GnRH analogues are given continually and continued after patients develop castration-resistant disease.

Persistence of Effect See Durability of Response.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

None

Additional Analyses Conducted on the Individual Trial

See above.

Integrated Review of Effectiveness

(b) (4)

8.1.3. Assessment of Efficacy Across Trials

Primary Endpoints

(b) (4)

The 3 Month Formulation of Lutrate Depot achieved and maintained castrate testosterone levels in 94.3% (95% CI: 89.4, 97.0) of patients. The lower bound is only 0.6% less than the required 90%. Further, one patient in this analysis was considered non-castrate due an insufficient sample for re-analysis, but had an original testosterone level < 50 ng/dL. The lower bound for the confidence interval of the sensitivity analysis in which this patient is considered castrate is > 90%. A larger sample size in all the trials of GnRH analogues would help to narrow the confidence intervals.

Secondary and Other Endpoints

Use of (b) (4) 3 Month Formulations resulted in a decrease in PSA.

Subpopulations

Subgroup analyses were not included in the statistical plan. The effect of age, race, and region on the development of castrate testosterone levels was examined as an exploratory analysis. Only values from Day 28 to 168 were examined. Note that the analysis of patients who received the 3 Month Formulation does not include patients who were considered non-castrate due to an insufficient sample for re-analysis.

(b) (4)

Table 15: Exploratory Subgroup Analysis

	(b) (4)	3 Month Formulation	
		N	# Non-castrate (%)
Age			
< 60		23	1 (4)
61-70		53	3 (6)
71-80		63	2 (3)
81-90[1]		24	0
Race			
African-American		49	1 (2)
Not African-American		113	5 (4)
Region			
United States		162	6 (4)
Outside the US		0	0

[1]1 patient was age 91

Additional Efficacy Considerations

None

8.1.4. Integrated Assessment of Effectiveness

(b) (4)

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety of the (b) (4) 3 Month Formulations was examined by review of the adverse event and laboratory datasets. (b) (4) AEs were collected at each visit and patients were asked to keep a diary in which they recorded adverse events (including local reactions) and concomitant medications. The patient diary was to be reconciled with the case report forms by the site.

Day 168 was the last follow up visit (b) (4) Day 168 occurred 30 days after the last dose of the (b) (4) 3 months after the last dose of the 3 Month Formulation. That is, the last visit did not occur 30 days after the physiologic effect of these sustained release formulations were no longer present.

8.2.2. Review of the Safety Database

Overall Exposure

See patient disposition above concerning the number of doses of the (b) (4) 3 Month Formulation administered.

Adequacy of the safety database

The number of patients exposed to the (b) (4) 3 Month Formulations is relatively small given the number of patients with advanced prostate cancer. (b) (4) Periodic Safety Update Reports were submitted providing (b) (4) 8,138 patient-years of exposure to the 3 Month Formulation. Further, the safety profile of GnRH agonists has seen well described with similar medications. Literature was not relied upon in the evaluation of clinical safety.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data integrity and submission quality are acceptable. The findings of the clinical site inspections were considered acceptable by the Office of Scientific Integrity. The organization of the submission is poor, but all elements essential to the review were identified. (b) (4) The AE dataset for the 3 Month Formulation contains incorrect flags. Both datasets include AEs that were reported to have occurred prior to the first dose, but which are reported to be related to study drug (e.g., hot flush). The quality of the narratives was poor.

Categorization of Adverse Events

(b) (4)

table. For the AE tables, the preferred terms in the dataset were used.

Table 16: Inaccurate Mapping of Adverse Events

Adverse Event Term	Applicant's Mapping	FDA Mapping
Swelling in both ankles	Musculoskeletal Disorders, Joint effusion	General Disorders, Edema peripheral
Chest pain(s) Retrosternal pain Tightness in chest	General Disorders, Chest pain	Cardiac Disorders, Chest pain
Night sweats and hot flashes	General Disorders, Night sweats	Night sweats and Hot flashes
Erythema and sore right upper buttock Redness/soreness at injection site	General Disorders, Injection site erythema	General Disorders, Injection site erythema Injection site pain
Soreness at injection site	General Disorders, Injection site irritation	General Disorders, Injection site pain

(b) (4)

With the 3 Month Formulation, AEs were reported and graded using CTCAE v3 from the time of study initiation.

Routine Clinical Tests

(b) (4)

With the 3 Month Formulation, safety laboratories were obtained at baseline and Days 28, 84, 112, and 168. Laboratories were graded as high, low, or normal.

The Applicant was asked to grade the laboratories using CTCAE v. 3 (since this was used for the AEs with the 3 Month Formulation). However, the normal ranges recorded for some of the laboratories appear to be incorrect.

8.2.4. Safety Results

Deaths

(b) (4)

3 Month Formulation: There were no deaths.

Serious Adverse Events

The table below provides information on Grade 1-4 serious adverse events (SAEs) that occurred by Day 168. (b) (4) Patients (b) (4) reported hyperglycemia. One patient who received the 3 Month Formulation developed diabetic ketoacidosis. The patient had a history of diabetes, but was on no medications at entry.

Table 17: Serious Adverse Events

(b) (4)	**3 Month Formulation N = 163**
All SAEs	12 (7%)
Cardiac Disorders	
Heart Failure	1
Myocardial Infarction	1
Sick Sinus Syndrome	0
Sinus Bradycardia	0
Gastrointestinal Disorders	
Diarrhea	1
Gastritis	0
Incarcerated Hernia	1
Rectal Hemorrhage	1
General Disorders	
Non-cardiac Chest Pain	1
Pyrexia	0
Infections	
Pneumonia	1
Metabolism and Nutrition	
Dehydration	1
Diabetes/Hyperglycemia/DKA	1
Hypokalemia	0
Malnutrition	0
Musculoskeletal Disorders	
Back Pain	0
Neoplasms	
Benign Neoplasm of Bladder	1
Lung Cancer	0
Nervous System Disorders	
Parkinson's Disease	0

	(b) (4)	3 Month Formulation N = 163
Syncope		3
Renal and Urinary Disorders		
Hematuria		0
Urinary Retention/Obstruction		0
Skin Disorders		
Bullous Pemphigoid		0
Surgical and Medical Procedures		
Anticoagulant Therapy		0
Brachytherapy		0
Fall		1
Knee Arthroplasty		0
Meniscus Lesion		0
TURP		0
Vascular Disorders		
Aortic Aneurysm		0

[1]This is grouped with Injury, Poisoning, and Procedural Complications

(b) (4)

- One patient who received the 3 Month Formulation was reported to have a bladder neck tumor. This was coded to the SAE benign bladder tumor. However, review of the narrative found that this patient did have malignant disease. It appears that obstruction was due to prostate cancer.

Grade 3-4 Adverse Events

There were (b) (4) 21 (13%) Grade 3-4 adverse events with the (b) (4) 3 Month Formulations, (b) (4)

There was one Grade 4 event among patients who received the 3 Month Formulation, diabetic ketoacidosis.

Dropouts and/or Discontinuations Due to Adverse Effects

Patients cannot discontinue prolonged release formulations in the typical sense of stopping oral or intravenous administration of study drug. However, patients can choose not to receive additional injections. (b) (4)

With the 3 Month Formulation, no patients were reported to have discontinued due to an AE. However, 1 patient who discontinued due to Patient/Investigator Decision reported hot flushes.

Significant Adverse Events

Local Reaction

(b) (4) the 3 Month Formulation, there were 36 reports in 23 patients. Most of the moderate and severe injection site reactions persisted for one day with one reaction persisting for 13 days.

Table 18: Local Reactions

	(b) (4)	**3 Month Formulation N = 163**
All		23 (14%)
Injection Site Pain/Discomfort		18
Injection Site Irritation		0
Injection Site Hemorrhage/Bruising		1
Injection Site Erythema		5
Injection Site Injury[1]		0
Injection Site Reaction[2]		0
Injection Site Swelling		0
Injection Site Induration		4
Injection Site Urticaria		1
Injection Site Warmth		1

[1]Stinging at the site of injection; [2]Hardening of the muscle at the site of injection

- (b) (4) With the 3 Month Formulation, injection site soreness and burning were mapped to injection site pain.

Hot Flush/Hyperhidrosis

The combined term (hot flush/flushing, hyperhidrosis, cold sweats, night sweats) occurred in (b) (4) 128 (79%) patients receiving the 3 Month Formulation. (b) (4) . Hot flushes and sweating are typically the most commonly reported AEs with GnRH analogues, but there are substantial differences in incidence between studies using the same dose and schedule. This suggests differences in study conduct.

Table 19: Hot Flush and Hyperhidrosis

	(b) (4)	3 Month Formulation N = 163
Hot Flush/Hyperhidosis		128 (79)
Hot Flush/Flushing		128 (79)
Hyperhidrosis[1]		8 (5)

[1]Includes cold sweats, night sweats

Adverse Events Related to Breast or Testicles

There were few reports of breast pain or enlargement; (b) (4) 1 report with the 3 Month Formulation. Additionally, there were few reports of testicular pain or atrophy; (b) (4) 4 reports with the 3 Month Formulation.

Fatigue

Fatigue/asthenia/malaise was reported in (b) (4) 15% of patients who received the 3 Month Formulation.

Cardiac Adverse Events

Cardiac adverse events were closely examined and GnRH analogues contain a Warning concerning Cardiovascular Disease. From the short-term small single arm studies used to obtain the approval of GnRH analogues, no conclusions can be drawn concerning an increase or decrease in cardiac events. Population-based studies have suggested an increase in ischemic disease with GnRH analogues.

Gonadotropin-releasing hormone analogues also contain a Warning concerning QT prolongation since a slight increase in the QT interval is seen with androgen deprivation. Among the patients who received the 3 Month Formulation, there was one report of Grade 1 ventricular arrhythmia in a patient with a history of coronary disease and a normal potassium on the day of the event.

The table below provides all Cardiac Disorders and cardiac-related disorders listed under Investigations. It also provides information on the General Disorders of chest pain or discomfort. The footnote below the table provides the AE terms and the table itself, the preferred term.

Table 20: Cardiac Disorders

	(b) (4)	3 Month Formulation N = 163
Cardiac Disorders		
Angina		1
Atrial Fibrillation		0
Cardiac Disorder NOS		1
Cardiac Failure		1
Mitral Valve Incompetence		1
Myocardial Infarction		1
Myocardial Ischemia		0
Sick Sinus Syndrome		0
Sinus Bradycardia		0
Tachycardia		1
Ventricular Arrhythmia		1
General Disorders		0
Chest Discomfort		1[2]
Chest Pain		0
Non-cardiac Chest Pain		1
Investigations		
EKG Abnormal NOS		1
QT Prolongation		1
QT Shortened		1
T Wave Inversion		1

[1]Chest heaviness, tightness in chest; [2]Tightness in chest
[3]Atypical chest pain (N=1), Chest pain(s) (4), left sided chest pain (1), retrosternal pain (1), thorax pain (1)

- Some of the reports of the General Disorder, chest pain/discomfort appear to be cardiac in origin.

Diabetes Mellitus/Hyperglycemia

(b) (4)

With the 3 Month Formulation, 3 of the 5 patients with reports of diabetes/hyperglycemia had a history of diabetes/hyperglycemia. One patient on the 3 Month Formulation developed diabetic ketoacidosis.

Treatment Emergent Adverse Events and Adverse Reactions

The table below provides information on Grade 1-4 AEs that occurred in at least 5% of patients

(b) (4)

During the first 28 days of dosing, a disorder in the musculoskeletal system, typically pain or discomfort, was reported in 20 (12%) and 23 (14%) patients who received the (b) (4) 3 Month Formulations, respectively. Within the first 28 days, there was (b) (4) u retention with the (b) (4) two reports with the 3 Month Formulation. Throughout the treatment period, there were three reports of urinary obstruction/retention with (b) (4) six reports with the 3 Month Formulation. (b) (4)

Table 21: Treatment Emergent Grade 1-4 Adverse Events in ≥ 5% of Patients in Either Trial

(b) (4)	3 Month Formulation N = 163 (%)	
	Grade 1-4	Grade 3-4
All	158 (97)	21 (13)
Gastrointestinal Disorders		
Abdominal Pain/Discomfort	13 (8)	0
Diarrhea	21 (13)	2 (1)
Constipation	15 (9)	0
Nausea	14 (9)	0
General Disorders		
Injection Site Reaction	23 (14)	0
Asthenia/Fatigue/Malaise	24 (15)	1 (0.6)
Edema/Peripheral Edema	6 (4)	0
Chest Pain/Discomfort/Non-cardiac CP	2 (1)	1 (0.6)
Infections and Infestations		
Upper Respiratory Infection[1]	28 (17)	0
Urinary Tract Infection	12 (7)	0
Musculoskeletal Disorders		
Arthralgia/Arthritis	18 (11)	0
Musculoskeletal Pain/Discomfort	6 (4)	0
Back Pain	10 (6)	0
Extremity Pain	14 (9)	0
Bone Pain	11 (7)	0
Nervous System Disorders		
Headache/Sinus Headache	12 (7)	1 (0.6)
Dizziness	12 (7)	0
Psychiatric Disorders		
Insomnia/Sleep Disorder	8 (5)	0
Renal Disorders		
Dysuria/Non-infective cystitis	6 (4)	0
Pollakiuria	20 (12)	0
	Grade 1-4	Grade 3-4

	(b) (4)	3 Month Formulation N = 163 (%)	
		Grade 1-4	Grade 3-4
Nocturia		14 (9)	0
Urinary Tract Pain		13 (8)	1 (0.6)
Skin Disorders			
Hyperhidrosis[2]		8 (5)	1 (0.6)
Pruritus/Generalized Pruritus		9 (6)	0
Vascular Disorders			
Hot Flush		128 (79)	5 (3)
Hypertension/BP Increased		10 (6)	1 (0.6)

[1]Includes influenza, influenza-like illness, nasal congestion, nasopharyngitis, rhinitis, rhinorrhea, upper respiratory tract congestion
[2]Includes cold sweats, night sweats

(b) (4)

- The AE dataset for the 3 Month Formulation contained two AEs (hot flush) with uncertain start dates that were considered treatment related. Again, these are included in the table.

Given the large number of adverse event that were considered unrelated as well as the precedent set with the approval of the Lupron Depot 6 Month Formulation, both treatment emergent and treatment related AEs will be included in the package insert. Relatedness was recorded as definite/certain, probably/likely, possible, unlikely/none, and not related. Adverse events reported to be definite, probably, or possible were considered related. These are shown in the table below. Note that the relationship between study drug and the AEs is poorly characterized. For example, three patients were reported to have unrelated injection site reactions (AE Term injection site soreness).

Table 22: Grade 1-4 Treatment-emergent and Treatment-related AEs in ≥ 5% of Patients-3 Month Formulation

3 Month Formulation N = 163 (%)				
	Treatment-emergent		Treatment-related	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
All	158 (97)	21 (13)	141 (87)	7 (4)
Gastrointestinal Disorders				
Diarrhea	21 (13)	2 (1)	2 (1)	0
Constipation	15 (9)	0	1 (0.6)	0
Nausea	14 (9)	0	4 (2)	0
Abdominal Pain/Discomfort	13 (8)	0	1 (0.6)	0
General Disorders				
Injection Site Pain/Discomfort	18 (11)	0	15	0
Asthenia/Fatigue	24 (15)	1 (0.6)	22 (13)	1 (0.6)
Infections and Infestations				
Upper Respiratory Infection[1]	28 (17)	0	0	0
Urinary Tract Infection	12 (7)	0	0	0
Musculoskeletal Disorders				
Arthralgia/Arthritis	18 (11)	0	2 (1)	0
Extremity Pain	14 (9)	0	0	0
Bone Pain	11 (7)	0	4 (2)	0
Back Pain	10 (6)	0	1 (0.6)	0
Nervous System Disorders				
Dizziness	12 (7)	0	2 (1)	0
Headache/Sinus Headache	12 (7)	1 (0.6)	1 (0.6)	0
Renal Disorders				
Pollakiuria	20 (12)	0	3 (2)	0
Urinary Tract Pain	13 (8)	1 (0.6)	2 (1)	1 (0.6)
Nocturia	14 (9)	0	3 (2)	0
Skin Disorders				
Pruritus/Generalized Pruritus	9 (6)	0	3 (2)	0
Vascular Disorders				
Hot Flush/Flushing[2]	128 (79)	5 (3)	127 (78)	5 (3)
Hypertension/BP Increased	10 (6)	1 (0.6)	0	0

[1]Includes influenza, influenza-like illness, nasal congestion, nasopharyngitis, rhinorrhea, upper respiratory tract congestion.
[2]Includes cold sweat, flushing, hot flush, hyperhidrosis, and night sweats.

Laboratory Findings

(b) (4) With the 3 Month formulation, laboratories were obtained at baseline, Days 28, 84, 112, and at the final visit. The Applicant did not provide CTCAE grading (b) (4) (b) (4). Since CTCAE v3 was used to grade the AEs in the study of the 3 Month Formulation, the Applicant was asked to grade laboratories (b) (4) using CTCAE v3. Laboratories with no normal range were removed, but laboratories with no units were included in the FDA analyses. Laboratories that increased at least 1 grade from baseline were included in the table below.

There were several concerns about the normal ranges provided. (b) (4) The CTCAE v 3 lists Grade 4 WBC values as < 1.0 x 10^9/L. However, in examining these 85 laboratory values, the results ranged from 3.4-14.2 x 10^9/L, suggesting that the normal range was recorded incorrectly. This also occurred with some of the normal ranges for lymphocytes and neutrophils. Hematology laboratories with an apparently incorrect normal range and values that would typically be within or near the normal range were considered normal (Grade 0). The CTCAE grading provides values for Grade 2-4 hematological events and these were applied to laboratories with an apparently incorrect normal range. The normal range for the chemistries appeared to be correct except that creatinine levels were below the lower limit of normal at 27 time points. This appears unlikely in this elderly population. These were considered to be in the normal range in this analysis.

Examining the laboratory values, a substantial percentage of patients on both studies developed anemia, generally Grade 1. Anemia is a common adverse event associated with GnRH analogues. In addition, a substantial percentage of patients on both studies developed hyperglycemia, increased cholesterol, and increased triglycerides. Metabolic syndrome is a concern with decreased testosterone. In the absence of a controlled trial, it is difficult to determine the extent to which this is due to androgen deprivation. Few patients developed Grade 3-4 liver function tests and no patients met laboratory criteria for Hy's law.

Table 23: Grade 1-4 Laboratory Abnormalities

	(b) (4)	**3 Month Formulation N = 163 (%)**	
		Grade 1-4	Grade 3-4
Hematology			
Leukopenia		23 (14.1)	0
Neutropenia		14 (8.6)	0
Lymphopenia		12 (7.4)	2 (1.2)
Anemia		60 (36.8)	0
Thrombocytopenia		13 (8.0)	0

	(b) (4)	3 Month Formulation N = 163 (%)	
		Grade 1-4	Grade 3-4
Chemistry			
Hyperglycemia		52 (31.9)	7
Increased Cholesterol		46 (28.2)	0
Increased Triglyceride		56 (34.4)	2 (1.2)
Increased AST		22 (13.5)	0
Increased ALT		17 (10.4)	0
Increased Bilirubin		4 (2.5)	0
Increased Alkaline Phosphatase		10 (6.1)	1 (0.6)
Increased Creatinine		19 (11.7)	0
Hypernatremia		8 (4.9)	4 (2.5)
Hyponatremia		10 (6.1)	1 (0.6)
Hyperkalemia		4 (2.5)	1 (0.6)
Hypokalemia		5 (3.1)	0
Hypercalcemia		11 (6.7)	0
Increased Creatine Kinase		29 (17.8)	1 (0.6)

[1]N = 158 for platelets, 140 for glucose, 157 for calcium

Vital Signs

The on-study vital signs are consistent with an elderly population with substantial co-morbid disease. Changes in vital signs did not contribute to the safety profile. (b) (4) seven on the 3 Month Formulation had a > 30 bpm difference between on-study and baseline heart rate. Most of the on-study heart rate were near the normal range. One patient on the 3 Month Formulation had a heart rate of 50 bpm and a pacemaker infection was reported. Systolic blood pressures > 160 (N=46) and diastolic blood pressures > 100 (N=4) during the treatment period were also examined. The majority of these patients had a history of hypertension.

Electrocardiograms (ECGs)

Wave forms were not submitted for evaluation by QT-IRT. There were no eligibility requirements concerning the QT interval in either study. (b) (4) With the 3 Month Formulation, EKGs were obtained at Days 0, 28, 84, 112, and 168. Low testosterone levels have been associated with a slight prolongation in the QT interval and GnRH analogues typically contain a Warning concerning QT prolongation.

(b) (4)

(b) (4) Among the patients who received the 3 Month Formulation, nine patients were also found to have a QTcF interval > 500 ms during the study period. Eight of the nine patients did not have a baseline value > 500 msec.

QT

See above.

Immunogenicity

Not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

The AEs that occurred during both trials are consistent with the AE profile of other GnRH agonists and no new safety signals were identified. Adverse events seen during the trials of the (b) (4) 3 Month Formulations of Lutrate Depot that have been associated with other GnRH analogues including tumor flare, hyperglycemia/diabetes, cardiovascular disease, and QT prolongation. Seizures were not seen. Hot flushes and injection site reactions were also reported. A small number of patients experienced an increase in muscle or bone pain during the first 28 days, but most patients had localized disease. Urinary retention was seen.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Patients who received the (b) (4) 3 Month Formulations were asked to complete a Bone Pain, Urinary Pain, and Urinary Symptoms questionnaire. These assessments asked them to rate, on a scale of 1 to 10 where 1 is no pain/symptoms and 10 is worst pain/symptoms, their symptoms. In all the tables below, the pain/symptom score is shown in the column on the left and the number of patients with that pain score is shown at various time points during the study period.

Most of the patients who received (b) (4) the 3 Month Formulation did so. For example, 157 patients received their 2nd dose of study drug on Day 84, but only 54 patients completed the questionnaire on Day 84. The questionnaires for the 3 Month Formulation are, therefore, uninterpretable due to a substantial amount of missing data.

Bone Pain

(b) (4) Among the nine patients with a bone pain score > 5, four reported a related adverse event. Two patients had a baseline bone pain score > 5. One of these patients had an initial increase and then a decrease to 2 by Day 4. However, the pain score increased again at Day 56

and subsequently decreased to 1-2. The other patient had pain scores of 5-8 throughout the treatment period.

(b) (4)

Among the patients who received the 3 Month Formulation, all patients reported a pain score of 1 on Days 2 and 14. This may be due to the presence of localized rather than metastatic disease in the majority of patients. Throughout the treatment period, four patients reported a bone pain score > 5. Two of the four reported related AEs. Examining pain scores over time, in the six patients with a pain score > 1 at baseline, five patients had subsequent scores of 1. The remaining patient had a decrease in pain score to 1 that rose to 10 on Day 56.

Table 25: Bone Pain-3 Month Formulation

	Baseline	**Day 2**	**Day 14**	**Day 28**	**Day 56**	**Day 84**	**Day 86**	**Day 112**	**Day 168**
N	**157**	**151**	**120**	**99**	**64**	**54**	**77**	**53**	**59**
Score									
1	151	151	120	99	62	50	74	52	59
2	2	0	0	0	0	1	0	0	0
3	3	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	1	0	0
5	0	0	0	0	0	1	1	1	0
6	1	0	0	0	0	1	0	0	0
7	0	0	0	0	1	1	1	1	0
8	0	0	0	0	0	0	0	0	0
10	0	0	0	0	1	0	0	0	0

Urinary Pain

Among the patients who received the 3 Month Formulation, there was one patients who reported a urinary pain score > 5 during the treatment period. This patient had a baseline value of 1 that rose to 10 on Day 2 and was reported as 1 from Day 28 onward. This patient reported urinary tract and pelvic pain and may have been an example of tumor flare. One patient reported a score of 2 at baseline and had subsequent scores of 1.

Table 27: Urinary Pain-3 Month Formulation

	Baseline	Day 2	Day 14	Day 28	Day 56	Day 84	Day 86	Day 112	Day 168
N	157	151	120	99	64	54	77	53	59
Score									
1	156	150	119	99	63	52	77	52	58
2	1	0	1	0	1	1	0	1	0
3	0	0	0	0	0	1	0	0	1
10	0	1	0	0	0	0	0	0	0

Urinary Symptoms

Among the patients who received the 3 Month Formulation, six had a urinary symptom score > 5 at some point during the treatment period. Two of these patients reported related AEs. Among the three patients with a urinary symptom score > 5 at baseline, one patient improved to a score of 1 and later again increased to 6, one improved to a score of 1, and the third had only 1 additional score recorded (also 7). Again, it is difficult to determine if urinary symptoms are related to the prostate cancer itself.

Table 29: Urinary Symptoms-3 Month Formulation

	Baseline	Day 2	Day 14	Day 28	Day 56	Day 84	Day 86	Day 112	Day 168
N	157	151	120	99	64	54	77	53	59
Score									
1	140	136	107	90	59	47	72	48	54
2	2	2	3	3	3	4	3	3	2
3	4	6	3	0	0	1	0	1	0
4	2	1	1	1	1	1	0	0	0
5	6	4	5	2	1	1	2	0	0
6	2	1	1	1	0	0	0	1	2
7	1	0	0	1	0	0	0	0	1
8	0	0	0	1	0	0	0	0	0
10	0	1	0	0	0	0	0	0	0

8.2.7. Safety Analyses by Demographic Subgroups

The tables below provide information on the incidence of AEs that occurred in > 10% of the population (b) (4) by race and age. (b) (4)

Race

The majority of patients were White. Here, race is broken down by White/Other. Grade 1-4 AEs were less likely to be reported by Whites with some increase in reports of hot flush among patients whose race was categorized as Other.

Table 30: Grade 1-4 Adverse Events in > 10% of Patients by Race

	White N = 243 (%)	Other N = 80 (%)
All	213 (88)	77 (96)
Arthralgia/Arthritis	24 (10)	11 (14)
Asthenia/Fatigue/Malaise	39 (16)	9 (11)
Hot Flush/Flushing	147 (60)	58 (73)
Injection Site Reaction	42 (17)	12 (15)

Age

Unlike most trials intended for approval, prostate cancer trials enroll an older population with few patients less than age 65. The difference in the incidence of Grade 1-4 AEs was small and the incidences of AEs such as fatigue or hot flushes were similar by age. Younger patients would

be expected to report a higher incidence of hot flush.

APPEARS THIS WAY ON ORIGINAL

Table 31: Grade 1-4 Adverse Events in > 10% of Patients by Age

	≥65 Years N = 246	< 65 Years N = 77
All	220 (89)	70 (91)
Arthralgia/Arthritis	24 (10)	11 (14)
Asthenia/Fatigue/Malaise	35 (14)	13 (17)
Hot Flush/Flushing	159 (65)	46 (60)
Injection Site Reaction	40 (16)	14 (18)

8.2.8. Specific Safety Studies/Clinical Trials

None

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Carcinogenicity studies were not conducted by GP Pharm, but the 505(b)(2) refers to carcinogenicity studies with leuprolide acetate conducted by other Applicants. Carcinogenicity studies in rats with leuprolide acetate found pituitary hyperplasia, pituitary adenomas, pancreatic islet cell adenomas, and testicular interstitial cell adenomas. Carcinogenicity studies in mice found no leuprolide acetate-induced tumors. The doses of leuprolide acetate used in these animal carcinogenicity studies was higher than the dose of leuprolide acetate used clinically. Humans have received 10-20 mg/d of leuprolide acetate for 2-3 years without demonstrable pituitary abnormalities.

Human Reproduction and Pregnancy

Again, these studies were conducted by other Applicants and referred to in the 505(b)(2). In rats, leuprolide acetate resulted in resulted in atrophy of the reproductive organs and suppression of reproductive function. These doses were lower than those used in humans. Changes in the reproductive organs were reversible after discontinuation of leuprolide.

Given leuprolide acetate, pregnant rabbits had an increase in major fetal abnormalities while pregnant rats had an increase in fetal mortality. Both studies used a dose of leuprolide acetate lower than that administered to humans.

To encourage exploration of the use anti-cancer agents in female patients, a decision has been made to no longer contraindicate GnRH analogues in pregnancy. Lutrate Depot will not, therefore, be contraindicated in pregnancy.

Pediatrics and Assessment of Effects on Growth

Not applicable

Lutrate Depot is only indicated in the palliative treatment of advanced prostate cancer. Prostate cancer is rarely or never seen in children.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable
Following discontinuation of Lutrate Depot or other GnRH agonists, males often have a prolonged period of testosterone suppression followed by normalization. The duration of testosterone suppression appears to be age dependent.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Pituitary apoplexy and decreased bone density have been noted in the postmarketing setting with GnRH agonists and these adverse reactions will be included in the Lutrate Depot package insert.

Periodic Safety Update Reports for Lutrate Depot (b) (4) 22.5 mg from August 2012 to July 2017 and August 2017 to June 2018 were reviewed. (b) (4) 8,138 patient-years of exposure to the 22.5 mg product.

Identified safety concerns listed in the PSUR include hypersensitivity reactions, testicular atrophy, gynecomastia, depression, suicide, hepatic dysfunction, sexual dysfunction, decreased libido, impotence, and pneumonitis/ILD.

With Lutrate Depot, anaphylaxis and pituitary apoplexy have been seen in the postmarketing setting.

Expectations on Safety in the Postmarket Setting

Outside the US, (b) (4) the 3 Month Formulation since 2015. Further, GnRH agonists have been marketed since the 1980s. Compared to other anti-cancer agents, GnRH agonists are well tolerated. It is unlikely that new postmarketing events will be identified. However, PSURs will be followed for the development of rare events.

8.2.11. Integrated Assessment of Safety

(b) (4)

[redacted]

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The statistical analysis plan for evaluating the primary endpoint was based on an exact two-sided binomial test. The percentage of patients who achieved and maintained castrate testosterone levels at Applicant pre-specified key time points was estimated with the exact method. This method could be affected by the amount of missing data at the key time points, since patients would be considered "successful" in achieving or maintaining castration if the missing data was assessed as unrelated to study drug. This may introduce bias in an open-label study since it was necessary to determine whether a missing data point was related or unrelated to study drug. The statistical plan did not discuss issues related to testosterone levels at the other time points. This again is problematic since a patient with a castrate testosterone level at a key time point would be considered "successful," but may have non-castrate testosterone levels at multiple other time points. To better address issues concerning missing data and testosterone surges in the study, it is more suitable to use the Kaplan-Meier method for analysis of the maintenance of castration.

8.4. Conclusions and Recommendations

(b) (4)

[redacted]

- **Lutrate Depot 22.5 mg (3 Month Formulation)**
    - Lutrate Depot 22.5 mg achieved and maintained castrate (≤ 50 ng/dL) testosterone levels in 94.3% (95% CI: 89.4, 97.0) of patients.
        - The lower bound of the 95% confidence interval, 89.4%, is slightly below the Agency standard of a lower bound of ≥ 90%. Note that one patient in this analysis was considered non-castrate due an insufficient sample for re-analysis, but that the remaining testosterone levels were ≤ 50 ng/dL. In a sensitivity analysis in which this patient was considered to have a castrate testosterone level, the lower bound of the 95% confidence interval was > 90%. A larger sample size in all the trials of GnRH analogues would help to narrow the confidence intervals.
    - The safety profile of Lutrate Depot 22.5 mg is consistent with other GnRH agonists.
        - There were no deaths during the study period.
        - One patient discontinued due to intolerable hot flushes.
        - Serious adverse events occurred in 7% and Grade 3-4 events in 13% of patients.
        - Grade 1-4 adverse events in > 10% of patients included: hot flushes, upper respiratory infection, fatigue, diarrhea, pollakiuria, arthralgia, and injection site pain.
        - Grade 1-4 laboratory abnormalities in > 20% of patients included: anemia, increased triglyceride, hyperglycemia, and increased cholesterol.
    - A Postmarketing Requirement to fully test syringe performance for the combination product, mannitol diluent in syringe will be issued. A Postmarketing Commitment concerning the development of an improved method for in vitro drug release testing has also been agreed to.
    - **Approval is recommended.**

X	X
Hui Zhang Primary Statistical Reviewer	Shenghui Tang, PhD Statistical Team Leader
X	X
Virginia Ellen Maher, M.D. Primary Clinical Reviewer	Virginia Ellen Maher, M.D. Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

There are several approved GnRH agonists and an Advisory Committee meeting was not needed.

10 Pediatrics

Since prostate cancer is not seen in pediatric patients, a pediatric waiver was requested and granted.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

FDA made revisions throughout the Lutrate labeling based on the most current efficacy and safety information available for leuprolide acetate for depot suspension products. (b) (4)

and Clinical and Statistical Evaluation). For complete details, see the final approved prescribing information (USPI) accompanying the NDA 205054 FDA approval letter.

Summary of Significant Labeling Changes		
Section	**Proposed Labeling**	**Approved Labeling** *(As of August 3, 2018)*
Highlights of Labeling		
See the corresponding revisions in the Full Prescribing Information.		
Full Prescribing Information (FPI)		
1. Indications and Usage	...	FDA removed (b) (4)
2. Dosage and Administration	(b) (4)	
	...	
3. Dosage Forms and Strengths	...	FDA revised to provide the dosage form (For Injection) and additional identifying characteristics required for LUTRATE DEPOT.
4. Contraindications	(b) (4)	

	(b) (4)	
5. Warnings and Precautions	5.6 Laboratory Tests …	FDA removed passive language that was inconsistent with the advice in this section regarding required laboratory monitoring.
5. Warnings and Precautions	5.7 Embryo-Fetal Toxicity (added by FDA)	FDA added the following: "5.7 Embryo-Fetal Toxicity Based on findings in animal studies, LUTRATE DEPOT may cause fetal harm when administered to a pregnant woman. In animal developmental and reproductive toxicology studies, administration of the monthly formulation of leuprolide acetate on day 6 of pregnancy (sustained exposure was expected throughout the period of organogenesis) caused adverse embryo-fetal toxicity in animals at doses less than the human dose, based on body surface area, using an estimated daily dose. Advise pregnant patients and females of reproductive potential of the potential risk to the fetus [*see Use in Specific Populations (8.1*)]."
6. Adverse Reactions	…	FDA added the cross reference to adverse reactions (ARs) discussed in more detail in the Warnings and Precautions sections of the labeling.
6. Adverse Reactions	6.1 Clinical Trials Experience …	FDA revised the clinical trial description for LUTRATE DEPOT 22.5 mg to add the duration of treatment (24 weeks), number of patients treated, and incidence of Grade 3-4 ARs. The AR table (Table 2) was revised to include

		treatment-emergent and treatment-related ARs with an incidence of ≥ 5%. Based on FDA safety review, Table 1 was revised to add ARs for upper respiratory tract infection, diarrhea, arthralgia/arthritis, constipation, extremity pain, nocturia, abdominal pain/discomfort, urinary tract infection, dizziness, headache, back pain, hypertension, and pruritus. The incidence rates for treatment-emergent and treatment related ARs were also revised based on FDA safety analysis. FDA added a statement to identify erectile dysfunction and testicular atrophy ARs that occurred in the study.
6. Adverse Reactions	6.2 Postmarketing Experience	FDA revised the proposed ARs to add anaphylaxis, depression, pneumonitis, and interstitial lung disease.
8. Use in Specific Populations	8.1 Pregnancy …	FDA removed (b) (4) FDA revised this section to add that the fetal harm risk with LUTRATE DEPOT was based on findings from animal studies and the mechanism of action. FDA removed (b) (4)
8. Use in Specific Populations	(b) (4)	8.2 Lactation FDA revised this section to inform HCPs that the safety and efficacy of LUTRATE DEPOT has not been established in women and there is no information regarding the presence of LUTRATE DEPOT in human milk, the effects on the breastfed child, or the effects on milk production.
8. Use in Specific	8.3 Females and	FDA added this subsection and the following to

Populations	Males of Reproductive Potential ...	this labeling: "Based on findings in animals and mechanism of action, LUTRATE DEPOT may impair fertility in males of reproductive potential [*see Nonclinical Toxicology (13.1)]."*
11. Description	...	FDA revised the Description section to provide the leuprolide acetate molecular weight as a free base, additional product characteristics, and route of administration.
14. Clinical Studies	14.1 LUTRATE DEPOT 22.5 mg for 3-Month Administration ...	FDA revised the study description for LUTRATE DEPOT 22.5 mg as follows: • Revised the evaluable population from (b) (4) patients to 162 patients and adjusted the efficacy results accordingly. • Removed (b) (4) • Added the following demographic and baseline disease characteristics: "The median age was 71 years (range; 47-91), 62% White, and 30% Black or African-American." FDA revised the study results description as follows: • (b) (4) • FDA removed (b) (4) • FDA removed (b) (4) • FDA also removed (b) (4) • FDA removed (b) (4)

		(b) (4)
15. References		Added "OSHA Hazardous Drugs. *OSHA.* http://www.osha.gov/SLTC/hazardousdrugs/index.html".
17. Patient Counseling Information	…	FDA revised this section to be consistent with the FDA Guidance for Patient Counseling Information (e.g., reformatted with counseling topics, cross references, and language directed to HCPs. FDA added information related to tumor flare, hyperglycemia, cardiovascular disease, infertility, and continuation of LUTRATE DEPOT with additional medications for prostate cancer as a counseling topics to this section.

12 Risk Evaluation and Mitigation Strategies (REMS)

There is substantial safety information concerning this product and concerning GnRH agonists. A REMS is not planned.

13 Postmarketing Requirements and Commitment

Postmarketing Requirement

The Applicant has not provided an adequate assessment of the performance characteristics of the pre-filled syringe containing mannitol (diluent). Syringe performance is a concern because one patient on the trial did not receive a full dose of study drug and because there have been reports of difficulties with administration with other products. The Applicant will, therefore, fulfill the following Postmarketing Requirement.

> Assess the break loose and glide force necessary for the safe administration of Lutrate Depot 22.5 mg with syringes that are at the beginning and end of their shelf life, and submit a final study report. Develop a standing protocol to control the essential performance characteristics and regular testing of the break loose and glide force, and dose accuracy for the combination product, pre-filled syringe containing 2 mL mannitol for injection.
>
> Final Report Submission: 02/2019

Postmarketing Commitment

The Applicant's method of in vitro drug release testing is acceptable on an interim basis. However, the Applicant has agreed to develop an improved method of in vitro drug release testing. The Postmarketing Commitment will read as follows:

> Development and validation of an accelerated in vitro drug release method and setting of the drug release acceptance criteria for Lutrate Depot (leuprolide acetate) 22.5 mg product.
>
> Interim Report: 02/2019
> Final Report: 08/2019
> Other (submit as PAS): 08/2019

The Applicant was asked to submit a meeting request at the time of submission of the interim report so that the findings can be discussed.

14 Division Director (OCP)

X

Atiq Nam Rahman, PhD
Division Director, OCP

15 Associate Division Director (OB)

X

Jason Schroeder, PhD
Associate Director, DBV

16 Deputy Division Director (Clinical)

X

Amna Ibrahim, MD
Deputy Division Director, DOP1

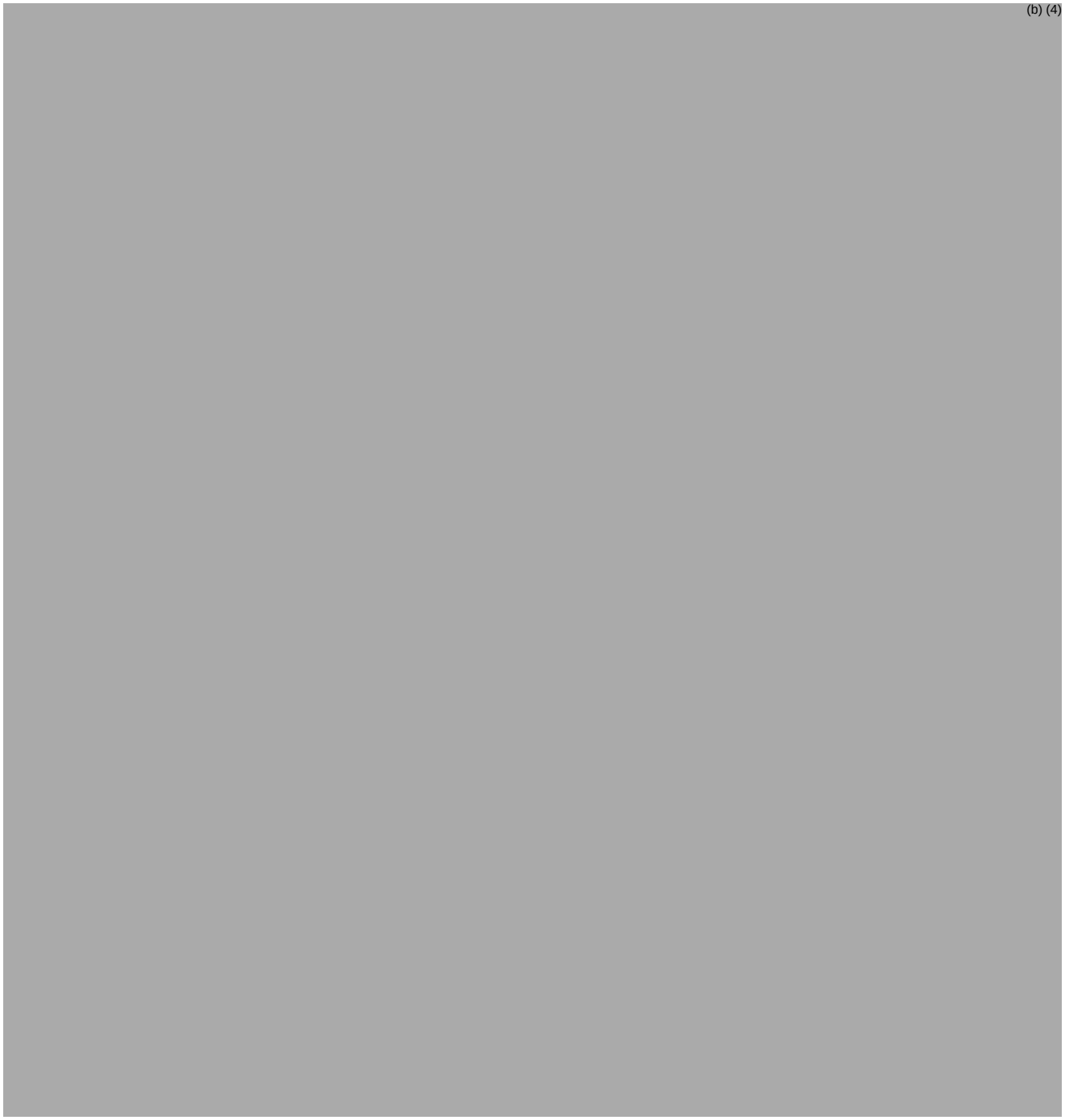
17 Appendices

17.1. References

Reference are included within the text.

17.2. Financial Disclosure

(b) (4)



Covered Clinical Study: GP/C/05/PRO-3 Month Formulation

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 29 principal investigators from sites that enrolled		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

17.3. Nonclinical Pharmacology/Toxicology

Not applicable

17.4. OCP Appendices (Technical documents supporting OCP recommendations)

17.4.1. Bioanalytical Methods

LEUPROLIDE

Study GP/C/05/PRO (22.5 mg)

Leuprolide plasma concentrations were measured in patients using a validated enzyme immunoassay (EIA) technique. Blood was collected in 10 mL PET tubes containing 25 μM PPACK, 4.5 mM EDTA and 500 KIU/mL aprotinin, and then centrifuged (1600 x g at 4°C for 15 minutes). Plasma was collected into PP tubes, divided into 2 aliquots and stored at -70°C or colder before analysis.

The characteristics of the bioanalytical method are summarized below (**Error! Reference source not found.**), based on the Validation report ((b) (4) Project Code: UX034) for "*Determination of Leuprolide in Human Plasma by EIA.*"

Table 33: Characteristics of the Validation Enzyme Immunoassay (EIA) Method Used to Measure Leuprolide Plasma Concentrations in Trial GP/C/05/PRO

Calibrated Range	0.050 – 2.00 ng/mL
Defined LLOQ	0.100 ng/mL
Defined ULOQ	1.75 ng/mL
Inter-assay Accuracy [bias %]	Between -3.4% and 11.6%
Inter-assay Precision [CV%] (ICH: Intermediate Precision)	Between 3.70% and 11.3%
Intra-assay Accuracy [bias%]	Between -13.7% and 27.6%
Intra-assay Precision [CV%] (ICH: Repeatability)	Between 0.433% (VSULOQ 2.00 ng/mL) and 10.7%

TESTOSTERONE

Upon the request of the Division of Oncology Products 1 (DOP1), the Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the bioanalytical assays used in the measurement of testosterone concentrations in the two pivotal Phase 3 trials. The OSIS inspection concluded that the bioanalytical assays used for the measurement of testosterone concentrations are acceptable.

(b) (4)

Phase 3 Study GP/C/05/PRO

Initial (Old) Method Validation

A total of 2066 human plasma samples (N=163) in Phase 3 Study GP/C/05/PRO were analyzed for the content of testosterone according to the bioanalytical method "*Quantitative Determination of Testosterone in Human Plasma by LC-MS/MS.*" Testosterone and the internal standard were extracted from plasma by liquid/liquid-extraction. The samples were analyzed by LC-MS/MS using Turbo Ion Spary Ionization and Multiple Reaction Monitoring (MRM). The standard curves were linear the measured range of 0.100 ng/mL to 10.0 ng/mL. The lower limit of quantification was 0.100 ng/mL using 0.250 mL plasma.

Table 35: Characteristics of the Initial LC/MS/MS Method Used to Measure Testosterone Plasma Concentration in Trial GP/C/05/PRO

Validated Parameter	**Testosterone**
Calibration Range (ng/mL)	0.250 – 10.0
LLOQ (ng/mL)	0.250
R^2 (overall mean)	0.99810
Inter-run precision* (%CV)	2.9 to 4.2
Inter-run accuracy* (%Bias)	5.8
Intra-run precision* (%CV)	0.8 to 2.6
Intra-run accuracy* (%Bias)	10.6
Selectivity	No problem
Matrix test	No problem
Stability in Plasma at room temperature	At least 24 hours
Stability after 3 Freezing/Thawing cycles	No problem
Stability of extracts of samples in a refrigerator ($5^oC \pm 3^oC$)	At least 72 hours
Stability of prepared samples at room temperature	At least 24 hours
Stability of prepared samples under autosampler conditions (~10^oC)	At least 72 days
Stability of prepared samples in a refrigerator ($5^oC \pm 3^oC$)	At least 72 days
Stability in plasma -$20^oC \pm 5^oC$	At least 15 days
Stability of analyte in stock solution	490 days at $5^oC \pm 3^oC$/6h at RT
Stability of analyte in working solution	490 days at $5^oC \pm 3^oC$/6h at RT
Stability of I.S. in the stock solution	496 days at $5^oC \pm 3^oC$/6h at RT
Stability of I.S. in the working solution	15 days at $5^oC \pm 3^oC$/6h at RT
Recovery	79% for analyte and IS
Matrix Effect	No effect observed
Dilution procedures	4-fold

Sample Reanalysis

Due to the interference observed in a small sub-group of samples (Figure 1) during the measurement of testosterone, the sponsor developed as modified method with a different mass transition (289→109). A comparison of the old (original) method and the new (modified) method used for sample reanalysis is summarized below (**Error! Reference source not found.**).

The Applicant relied on the validation of the original method and modified it with respect to testosterone specific mass transfers and partially revalidated the modified (new) method (validaton-report-TX005-Amend05). The re-validation experiments "matrix effect," "inter- and intra-run accuracy and precision," "out of range dilution," and "selectivity" were performed. A summary of the revalidation results is provided below (

Table 36: A Comparison of Re-validation Results of the Modified Method to the Original Method

).

Table 36: A Comparison of Re-validation Results of the Modified Method to the Original Method

Validated Parameter	Modified Method (mass transition 289 -> 109)	Original Method (mass transition 289 ->97)
Inter-run precision	cv = 2.0% to 14.5%	cv = 2.2% to 10.7%
Inter-run accuracy	bias = -4.3 to -1.8%	bias = -4.9 to 4.4%
Intra-run precision	cv = 1.5% to 8.2%	cv = 0.6% to 10.6%
Intra-run accuracy	bias = -3.7 to 8.2%	bias = -3.6 to 1.8%
Out of range dilution (DF= 4)	cv = 1.5%	cv = 1.5%
Out of range dilution (DF= 4)	bias = -6.2	bias = -8.2
Selectivity	acceptance criteria	acceptance criteria
Matrix effect (IS-normalized)	1.0155 (cv < 15.0%)	1.0131 (cv < 15.0%)

Table 37: Comparison of Original and Modified Bioanalytical Methods for Quantitative Determination of Testosterone in Human Plasma Samples

Parameter	Original Method	Modified Method
Analyte	Testosterone	
Internal Standard (IS)	d3-Testosterone	
Plasma sample volume	250 µL	
Extraction	Liquid-liquid	
HPLC		
Column	Phenomenex Gemini C18, 50x3.0 mm, 5 µm	
Injection volume	20 µL	
Mobile phase flow rate: 0.300 mL/min	0.15% Formic acid-Methanol	
Run time (min)	4.70	4.70
MS Conditions		
Mass spectrometer	AB Sciex API 3000	
Ion Source	Turbo Ion Spray	
Polarity run time	positive ions	
Mother ions	m/z= 289,1 (Testosterone)	
	m/z= 292,1 (IS)	
MRM mass ranges	**m/z= 97,0 (Testosterone)**	**m/z= 109,0 (Testosterone, quantitative)**
	m/z= 97,0 (IS)	m/z= 97,0 (IS)
		m/z= 97,0 (Testosterone, qualitative)
		m/z= 257,2 (Non-Testosterone specific)
Calibration range	0,100-10,0 ng/mL	
LLOQ	0,100 ng/mL	
QCs	0,300 ng/mL; 2,00 ng/mL ; 8,00 ng/mL	
Samples analyzed	2066	2057

17.4.2. OSIS Report

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 10, 2018

TO: Julia Beaver, M.D.
Director
Division of Oncology Products (DOP1)
Office of Hematology and Oncology Products
Office of New Drugs

William Chong, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Office of New Drugs

Atiqur Rahman, Ph.D.
Director
Division of Clinical Pharmacology V
Office of Clinical Pharmacology
Office of Translational Sciences

FROM: Gajendiran Mahadevan, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDBE
OSIS

SUBJECT: Surveillance inspection of [redacted] (b) (4)

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the analytical portion of [redacted] (b) (4) GP-C-05-PRO (NDA 205054) conducted at [redacted] (b) (4)

Form FDA 483 was issued at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI).

Significant objectionable conditions were observed during this inspection that impacted the reliability of a portion of data

from study GP-C-05-PRO. (b) (4)

(b) (4)

17.5. Additional Clinical Outcome Assessment Analyses

See above.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JANICE H KIM
08/21/2018

EIAS A ZAHALKA
08/21/2018

TIFFANY RICKS
08/21/2018

HUIMING XIA
08/21/2018
Sign on behalf of Dr. Salaheldin Hamed.

NAM ATIQUR RAHMAN
08/22/2018
I agree with the recommendation.

HUI ZHANG
08/22/2018

SHENGHUI TANG
08/22/2018

ROBERT J SCHROEDER
08/22/2018

AMNA IBRAHIM on behalf of VIRGINIA E MAHER
08/23/2018
Signed on behalf of Dr Virginia (Ellen) Maher

AMNA IBRAHIM
08/28/2018
All disciplines recommend approval for the 22.5 mg formulation. This formulation will be approved with two PMCs. (b) (4) I concur with these recommendations.

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Geoffrey Kim, MD
Subject	Division Director Summary Review
NDA/BLA # Supplement #	205054/0
Applicant Name	GP Pharm, S.A.
Date of Submission	July 31, 2014
PDUFA Goal Date	May 31, 2015
Proprietary Name / Established (USAN) Name	Lutrate Depot/leuprolide acetate
Dosage Forms / Strength	(b) (4) 22.5 mg for intramuscular injection
Proposed Indication(s)	Palliative treatment of advanced prostate cancer
Action/Recommended Action for NME:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Yangmin M Ning
Statistical Review	Hui Zhang
Pharmacology Toxicology Review	Eias Zahalka
CMC Review/OBP Review	Li-Shan Hsieh
Microbiology Review	Neal Sweeny
Clinical Pharmacology Review	Pengfei Song
OSI	Lauren Iacono-Conners
CDTL Review	Virginia Ellen Maher
Biopharmaceutics Review	Sandra Suarez Sharp

OND=Office of New Drugs
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader

1. Introduction

This New Drug Application (NDA 205054) for leuprolide acetate for intramuscular injection was submitted by GP Pharm S.A. under the provisions of 505(b)(2). The application relies on FDA's previous findings regarding nonclinical and safety data for the listed drug, Lupron

Depot (leuprolide acetate for depot suspension) manufactured for AbbVie Inc. by Takeda Pharmaceutical Company. The listed drug, Lupron Depot, was approved in 1989 and is marketed as a prefilled dual-chamber syringe containing sterile lyophilized microspheres which, when mixed with diluent, becomes a suspension intended as a monthly (7.5 mg) or every three month (22.5 mg) intramuscular injection. Leuprolide Acetate (GP Pharm) contains the same active ingredient, proposed route of administration and proposed indications as the listed drug, Lupron.

There are several major issues with this application pertaining to several disciplines. Major CMC deficiencies pertain to (b) (4)

2. Background

Androgen deprivation is the main therapeutic approach for men with advanced prostate cancer. Androgen deprivation can be achieved surgically by castration or by the use of various medical treatments. Luprolide acetate is LHRH (GnRH) analog that acts as an agonist on the GnRH receptors in the pituitary gland. Androgen suppression is achieved by disrupting the normal pulsatile stimulation of the GnRH receptors. The initial agonist activity causes a transient surge in lutenizing hormone (LH), follicle stimulating hormone (FSH), and testosterone. This surge typically occurs and resolves within the first 28 days of treatment. Following the initial surge of testosterone, it would be expected that androgen levels would be suppressed and remain suppressed without further surges throughout the course of treatment.

The achievement and maintenance of castrate testosterone levels is an accepted endpoint for the approval of GnRH agonists. For recent approvals of GnRH agonists, the lower bound of the 95% confidence interval of the percentage of patients achieving and maintaining castrate testosterone levels has been greater to equal than 87%. In addition, in other recent applications (Trelstar 22.5 mg IM and Lupron 45 mg IM), testosterone levels were drawn to assess the potential for unanticipated testosterone surges. The CDTL and combined clinical/statistical reviews delve in further details regarding the past approvals of other GnRH agonists.

Regulatory History
IND 72,790 was submitted in 2005. A Type C meeting was held in December 2005 to discuss the development of (b) (4) formulations. A pre-NDA meeting was held in October 22, 2012 to discuss the anticipated NDA submission. In the meeting minutes, FDA stated that the applicant should establish (b) (4) their proposed drug product and each listed drug upon which they propose to rely. The applicant was also asked to provide a Kaplan-Meier estimate

of the proportion of patients achieving castrate testosterone levels from Day 29 to 168. On July 31, 2014, FDA received the NDA.

3. CMC/Device

I concur with the conclusions reached by the chemistry and biopharmaceutics reviewers that there are outstanding issues which preclude product approval at this time. The chemistry and biopharmaceutics related deficiencies are summarized as follows:

(b) (4)

I also concur with the conclusions reached by the compliance reviewers that there are outstanding issues which preclude product approval at this time. The Division of Inspectional Assessment recommends withhold for the following reasons:

(b) (4)

4. Nonclinical Pharmacology/Toxicology

From the Pharmacology/Toxicology review, "the Lutrate Depot formulation contains an excipient, triethyl citrate (TEC), that was not previously characterized when administered by the intramuscular route. TEC is listed in the FDA Inactive Ingredients Search for Approved Drug Products and is contained at a maximum potency (b) (4) in an oral, delayed-action tablet. The safety profile of intramuscularly administered TEC was therefore characterized in a single- /repeat dose (28-day) toxicology study in rats at doses which exceed that expected clinically. No adverse toxicity was reported in the TEC-treated animals. Based on this data and previous experience in approved drugs containing TEC for oral administration, this excipient was considered qualified at the specified level for intramuscular injection in Lutrate Depot."

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology

From the clinical pharmacology review: "The applicant submitted the results of (b) (4) open-label, single-arm Phase 3 trial (b) (4) Study GP/C/05/PRO for 22.5 mg in 163 patients). Pharmacokinetic (PK) data available from (b) (4) 30 patients in Study GP/C/05/PRO indicated that maximum plasma concentration (Cmax) of leuprolide was achieved in approximately 2 hour after intramuscular injection. No obvious accumulation in plasma leuprolide concentrations was observed after repeated doses of both strengths of LUTRATE DEPOT.

The Office of Scientific Investigation (OSI) inspection concluded that the bioanalytical assays used for the measurement of testosterone concentrations are acceptable."

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

The Applicant has conducted the following (b) (4)

(b) (4)

- GP/C/05/PRO: Efficacy and Safety of a New Leuprolide Acetate 22.5 mg Depot Formulation in the Treatment of Prostate Cancer.

(b) (4)

(b) (4)

Study GP/C/05/PRO was an open-label, single-arm study of GP-Pharm's Lutrate (leuprolide acetate 22.5 mg) in patients with histologically proven carcinoma of the prostate who might benefit from medical androgen deprivation therapy. The primary endpoint was the proportion of patients with testosterone < 50 ng/dl on Days 28, 84, and 168 over the total number of patients with testosterone levels on at least one of those dates. Patients who were missing data (for reasons unrelated to study drug) at these key time points were considered to have maintained a castrate testosterone level.

Patients received Lutrate 22.5 mg intramuscularly on Day 0 and Day 84, and their testosterone levels were assessed at the protocol specified time points from Day 0 through Day168. One hundred and sixty three (163) patients were enrolled and 151 patients completed the study. The Applicant has included 161 patients in the primary analysis population. This population excludes 1 patient who discontinued on Day 3 and a second patient (S00117) who discontinued on Day 56 while he was receiving radiation therapy.

(b) (4) the FDA analysis of the primary endpoint differed from that of the applicant in that all available testosterone levels between Days 28 and 168 were included in the primary analysis. In addition, in the FDA analysis, if a single data point was missing and the testosterone levels before and after that data point were < 50 ng/dL, the patient was considered to have a castrate testosterone level at the missing time point. If two consecutive data points were missing, the patient was censored in the Kaplan-Meier analysis at the last available time point. This method prevents the imputation of multiple time points (as in a last observation carried forward analysis). Further details regarding the differences in the FDA and applicant's analysis of the primary endpoint can be found in the primary

clinical/statistical joint review. According to the FDA analysis which incorporates all available data the percentage of patients who achieved and maintained castrate testosterone levels was 83.9% (95% CI: 77.3, 88.8) which differs from the results of the applicant's analysis which reports the percentage of patients who achieved and maintained castrate testosterone levels was 98.1% (95% CI: 94.7, 99.6).

(b) (4) the percentage of patients who achieved and maintained castrate testosterone levels was far lower in the FDA's analysis as compared to the applicant's analysis. I agree with the primary clinical and statistical reviewer's assessment tha (b) (4) in this NDA were not efficacious in maintaining castration during an approximately 5-month maintenance period. This was due primarily to a large number of testosterone surges that were detected after a repeat dose. Given the (b) (4)% overfill of study product in the clinical batches and the questionable dose uniformity in their manufacturing, the detected testosterone surges may reflect issues concerning the product quality and/or leuprolide release equilibrium and efficiency from the suspension depots. Because of the CMC issues, the reviewers are concerned about the interpretability of clinical data and/or the reliability of the analyses based on the submitted data."

Safety

(b) (4) One hundred and sixty three (163) patients received at least 1 dose of the 3 month formulation and 157 received both injections of study drug. Common adverse events in the two studies were hot flushes, arthralgia, fatigue, injection site pain or discomfort, headache, and diarrhea. The majority of the adverse events were mild or moderate (b) (4) Grade 1-2 in Study GP/C/05/PRO. Important laboratory abnormalities were hyperglycemia, increases in hepatic transaminases and serum creatinine. The majority of the abnormalities were Grade 1-2. Severe hyperglycemia (Grade 3 or 4) was found in approximately 6% of patients in each study. The observed adverse events and laboratory abnormalities were consistent with the known safety profile of other GnRH analogs. I agree with the primary clinical reviewer and CDTL's assessment that the adverse event profile of Lutrate is comparable to other GnRH agonists.

8. Advisory Committee Meeting

Not Applicable

9. Pediatrics

Since prostate cancer does not occur in children, a pediatric waiver has been granted.

10. Other Relevant Regulatory Issues

OSI Clinical Inspections
Three clinical sites were chosen for inspection. For Study GP/C/05/PRO Site 1 (Dr. Neal

Shore, Myrtle Beach, SC) and Site 24 (Dr. Laurence Belkoff, Bala Cynwyd, PA) were inspected. [redacted] These sites were selected for inspection based on enrollment of large numbers of study subjects and significant primary efficacy results pertinent to decision making.
Based on the review of inspectional findings for clinical investigato [redacted] Dr. Belkoff (Study GP/C/05/PRO, Site 24), the data for [redacted] GP/C/05/PRO appear reliable.

There are no other unresolved relevant regulatory issues

11. Labeling

Review of the labeling will be completed during the next cycle or when the application is otherwise approvable.

12. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Complete Response

- Risk Benefit Assessment

Numerous deficiencies related to chemistry and manufacturing were identified that preclude approval of this application. In addition, the clinical trial results submitted to support the approval [redacted] failed to demonstrate efficacy in terms of the percentage of patients achieving and maintaining castrate testosterone levels from Day 28-168. Although prostate cancer is ultimately a lethal disease, androgen deprivation is able to control the disease process for a relatively long period of time in men with both localized and metastatic prostate cancer and there are several GnRH agonists that are currently approved that have demonstrated efficacy in terms of achieving and maintaining castrate testosterone levels. The concerns regarding quality and manufacturing of the drug product together with the lack of efficacy demonstrated in the clinical trials warrant a complete response until these issues are addressed. I agree with the clinical and statistical review team that based on the available data submitted in the NDA, an unfavorable risk-benefit profile has been demonstrated for [redacted] Lutrate and that following the resolution of the CMC, Biopharmaceutics, and compliance deficiencies, the applicant would be required to conduct additional clinical trials to demonstrate the safety and efficacy of their product.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

None

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/s/

GEOFFREY S KIM
05/29/2015

Cross-Discipline Team Leader Review

Date	May 28, 2015
From	Virginia Ellen Maher, M.D.
Subject	Lutrate Depot (b) (4) 22.5 mg
NDA/BLA # Supplement#	205054/0
Applicant	GP Pharm, S.A.
Date of Submission	March 18, 2014
PDUFA Goal Date	May 31, 2015
Proprietary Name / Established (USAN) names	Lutrate Depot/leuprolide acetate
Dosage forms / Strength	(b) (4) 22.5 mg for intramuscular injection
Proposed Indication(s)	Palliative treatment of advanced prostate cancer
Recommended:	Complete Response

Addendum

Based on the facilities inspection of GP Pharm, S.A., the Division of Inspectional Assessment recommends withhold for NDA 205054. This will be noted in the complete response letter. Please see withhold memorandum for complete information on the deficiencies. Briefly, these included:

(b) (4)

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/s/

VIRGINIA E MAHER
05/28/2015

Cross-Discipline Team Leader Review

Date	December 17, 2014
From	Virginia Ellen Maher, M.D.
Subject	Lutrate Depot (b) (4) 22.5 mg
NDA/BLA # Supplement#	205054/0
Applicant	GP Pharm, S.A.
Date of Submission	March 18, 2014
PDUFA Goal Date	May 31, 2015
Proprietary Name / Established (USAN) names	Lutrate Depot/leuprolide acetate
Dosage forms / Strength	(b) (4) 22.5 mg for intramuscular injection
Proposed Indication(s)	Palliative treatment of advanced prostate cancer
Recommended:	Complete Response

1. Introduction

NDA 205054, contains the following (b) (4)

(b) (4)

- GP/C/05/PRO administered 22.5 mg of leuprolide acetate every 3 months to 163 patients.

(b) (4) Lutrate Depot 22.5 mg IM every 3 months for the indication: palliative treatment of advanced prostate cancer.

2. Background

Gonadotropin releasing hormone (GnRH) agonists such as leuprolide acetate cause a transient surge in luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone (T). This surge desensitizes the LH and FSH receptors and is followed by a sustained decrease in testosterone to levels similar to those achieved following orchiectomy. Prostate cancer is an androgen responsive tumor and low testosterone levels result in cancer shrinkage. Over time, parts of the tumor can become hormone independent and these cells grow despite low levels of testosterone. However, other parts of the tumor can remain hormone sensitive. Thus, GnRH agonists are used in both hormone-sensitive and castration-resistant disease.

The approval of GnRH agonists for use in prostate cancer has been based on their ability to achieve and maintain castrate testosterone levels. The initial testosterone surge typically occurs and resolves within the first 28 days and castrate testosterone levels are measured from Day 28 until the end of study. The study duration is based on the dosing interval and typically extends through 2 or 3 administrations of the GnRH agonist. Achievement and maintenance of castrate testosterone levels is typically measured:

- Prior to the next dose-This permits an assessment of the drug's ability to maintain castrate testosterone levels over the entire dosing interval.

- 1-3 days after the second or subsequent dose of the GnRH agonist-This permits an assessment of the drug's ability to fully desensitize the LH and FSH receptors and to maintain castrate testosterone levels following additional stimulation with a GnRH agonist. If the LH and FSH receptors are not completely desensitized, an increase in testosterone to non-castrate levels will occur. This is referred to as the acute-on-chronic effect.

The clinical consequences of an increase in testosterone just prior to the next dose or following the second or later injections are not known. However, Applicants have been asked to evaluate these time points and to obtain approval GnRH agonists are expected to maintain castrate testosterone levels at these time points.

The timing of the testosterone levels and their use in the analysis of the primary endpoint, achievement and maintenance of castrate testosterone levels, is a major issue in the current application. Since transfer of the GnRH agonists to the Office of Hematology and Oncology Products, Trelstar 22.5 mg IM every 6 months and Lupron 45 mg IM every 6 months have been approved. Note that 60/120 patients in the study supporting the Trelstar 6 month formulation had testosterone levels drawn to assess the acute on chronic effect. In the study supporting the Lupron 6 month formulation, the acute on chronic effect was assessed in all patients. These studies can serve as examples of current expectations for the achievement and maintenance of castrate testosterone levels. The table below also provides information on previous approvals of GnRH agonists, the timing of testosterone assessments, and the results which led to their approval. The information in this table is limited to that in reviews posted on the FDA website and in package inserts and does not include all GnRH agonists, but is limited to formulations of leuprolide acetate.

(b) (4)

Regulatory History

(b) (4)

In July 2011, the Applicant submitted the study of the 3 month formulation of Lutrate Depot that has been submitted in this application. In October 2012, a

pre-NDA meeting was held for this application. At that time, the Applicant was asked to include the results of their pre-specified primary analyses from (b) (4) study in the NDA submission. The applicant was also asked to provide a Kaplan-Meier estimate of the proportion of patients achieving castrate testosterone levels from Day 29 to 168.

3. CMC/Device

(b) (4)

3 Month Formulation

In the 3 month formulation, (b) (4) The biodegradable polymer is response for the sustained release of leuprolide over the 3 month period.

(b) (4) the drug product is a lyophilized powder that is reconstituted with diluent within the MIXJECT delivery device and administered intramuscularly. CDRH was consulted concerning the delivery device for this application and found no deficiencies.

Numerous CMC deficiencies have been found in this application. Please see final letter to the Applicant for a list of these deficiencies. The essence of the CMC deficiencies is as follows:

(b) (4)

The Applicant provides a (b) (4)% overfill in drug product to account for drug release/loss during manufacturing. Thus, patients may receive substantially different amounts of study drug with each injection.

4. Nonclinical Pharmacology/Toxicology

(b) (4) . The Applicant also conducted a nonclinical study (b) (4) it was thought that Lutrate Depot 22.5 mg could also rely on the nonclinical information from the Lupron Depot NDA.

5. Clinical Pharmacology/Biopharmaceutics

(b) (4)

3 Month Formulation

Pharmacokinetic data are available for 30 patients treated with the 3 month formulation. These parameters were assessed after the first and second dose of study drug and their means and standard deviations are shown in the table below.

Table 3: 3 Month Formulation-Pharmacokinetic Parameters			
	C_{max} (ng/mL)	T_{max} (days)	AUC_{0-t} (ng/mL·hr)
Days 1-84	46.8 ± 18.0	0.1 ± 0.1	1,696.7 ± 963.5
Days 84-168	48.3 ± 18.6	0.1 ± 0.1	2,328.8 ± 1,134.0

The coefficient of variation for the AUC ranged from 48.5-56.8% for the first 2 doses.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

The Applicant has conducted the following (b) (4)

(b) (4)

- GP/C/05/PRO: Efficacy and Safety of a New Leuprolide Acetate 22.5 mg Depot Formulation in the Treatment of Prostate Cancer.

In this review, (b) (4) a discussion of the study design and efficacy of the 3 month, 22.5 mg formulation. In the Safety Review, the (b) (4) 3 month formulations will be discussed (b) (4).

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(b) (4)

3 Month Formulation

GP/C/05/PRO was conducted from October 2011 to May 2013 and enrolled 163 patients at 25 sites in the US.

Eligibility:

1. Patients with carcinoma of the prostate who might benefit from medical androgen deprivation
2. No evidence of impending spinal cord compression, impending urinary tract obstruction, or severe pain from extensive bone metastases
3. No previous GnRH analog use for > 6 mos and none within 12 mos of study entry; No androgen receptor blockers within 3 mos of entry; No 5-alpha-reductase inhibitors within 3 mos of entry; No alternative therapies which have an estrogenic or anti-androgenic effect within 3 mos of entry
4. No local, curative therapy to the primary tumor within 2 weeks of entry; Study drug may be given as neo-adjuvant therapy if local therapy does not start until 2 weeks after study completion
5. Life expectancy of $\geq$ 1 year, ECOG PS 0-2
6. Testosterone level above the LLN; adequate bone marrow, renal, and liver function

Treatment:

Leuprolide acetate 22.5 mg IM Day 0 and 84

Monitoring:

- Testosterone levels were obtained at baseline, Day 0 (prior to dosing and 1 and 4 h post-dose), Days 2, 14, 28, 56, *84* (prior to dosing and 1 and 4 h post-dose), 86, 112, and *168*.
    - Samples on the day of dosing (italics) were obtained prior to dosing. These samples will assess the duration of efficacy of the study drug.
    - For the Day 84 injection, samples were obtained at 1 and 4 h post-dose and on Day 86. These samples will assess the acute-on-chronic effect of study drug.
    - Samples were stored at $\leq$ -20^0 C at (b) (4) and then shipped to (b) (4) for the testosterone assay. The testosterone assay used liquid chromatography and mass spectroscopy. The lower limit of quantitation was 0.1 ng/mL in plasma.
- Safety laboratories were obtained at baseline and at Days 28, 84, 112, and 168.

Statistical Plan:
The primary endpoint was the proportion of patients with testosterone ≤ 50 ng/dl on Days 28, 84, and 168 over the total number of patients with testosterone levels on at least one of those dates. Patients who were missing data (for reasons unrelated to study drug) at these key time points were considered to have maintained a castrate testosterone level. The study drug would be considered successful if > 93% of patients achieved castrate testosterone levels on these dates.

Disposition
One hundred and sixty three (163) patients were enrolled and 151 patients completed the study. The Applicant has included 161 patients in the primary analysis population. This population excludes 1 patient who discontinued on Day 3 and a second patient (S00117) who discontinued on Day 56 while he was receiving radiation therapy. The study report states that the investigator who enrolled this patient was unresponsive to queries, as a result this patient was considered to have had a major protocol violation, and this patient was, therefore, not included in the primary analysis population. No patients discontinued due to an adverse event.

Baseline Characteristics
Median age was 72 years and 30% of patients were Black. Data concerning the presence of metastatic disease was available for 160 patients and 18 patients had metastatic prostate cancer

Primary Endpoint
The table below provides the results of the Applicant and FDA analyses of the percentage of patients with castrate testosterone levels.

Applicant: The Applicant's analysis included testosterone levels from Days 28, 84 and 168. The analysis population included 161patients (see Disposition).

FDA: The FDA analysis included patients who received study drug and who had testosterone levels available on Day 28. Day 28 was chosen because GnRH agonists typically achieve castrate testosterone levels by Day 28. The 1 patient who discontinued prior to Day 28 was not included in the analysis. The analysis period extended from Day 28 to Day 168. Day 168 was the last on-study visit.

The FDA analysis included all testosterone levels between Days 28 and 168. Inclusion of all time points resulted in 26 patients with non-castrate testosterone levels. In 17 patients, castrate testosterone levels were not maintained during/at the end of the dosing interval. This includes patients who did not have castrate testosterone levels at Days 28, 56, 84 (prior to dosing), 112, or 168. In 11 patients castration was not maintained during the acute-on-chronic period. That is, Day 84 1 hr and 4 hr post dosing and Day 86. Note that some patients, both an acute-on-chronic surge and non-castrate levels over/at the end of the dosing interval were seen.

The handling of missing data in the FDA analysis (b) (4) This method was described above for the 1 month formulation.

Table 5: 3 Month Formulation-Primary Analysis		
	Applicant's Analysis N = 161	FDA Analysis N = 162
Percentage with Castrate Testosterone Levels (95% CI)	98.1% (94.7, 99.6)	83.9% (77.3, 88.8)

Using all the available data, the percentage of patients who achieved and maintained castrate testosterone levels was far lower than products which have recently been approved.

8. Safety

Exposure

(b) (4)

One hundred and sixty three (163) patients received at least 1 dose of the 3 month formulation and 157 received both injections of study drug.

Deaths and Discontinuations

(b) (4)

No patients died during the trial involving the 3 month formulation.

(b) (4)

Adverse Events

(b) (4)

The table below provides information on treatment emergent adverse events that occurred in at least 10% of patients. CTC AE version 3 was used for adverse events grading. Treatment related adverse events (at least possibly related per Investigator) are also reported for this single arm study. Note that in 3 patients injection site pain/discomfort was considered unrelated to study drug (18 vs. 15 patients). This raises concern about the quality of data collection.

Table 7: 3 Month Formulation-Treatment Emergent Adverse Events in ≥ 10% of Patients				
	Treatment Emergent N = 163		Treatment Related N = 163	
	Grade 1-4	Grade 3	Grade 1-4	Grade 3
Vascular Disorders				
Flushing/Hot Flush	126 (77%)	5 (3%)	125 (77%)	5 (3%)
General Disorders				
Fatigue/Asthenia	24 (15%)	1 (0.6%)	22	1 (0.6%)
Injection Site Pain/Discomfort	18 (11%)	0	15 (9%)	0
Gastrointestinal Disorders				
Diarrhea	21 (13%)	2 (1%)	2 (1%)	0
Renal and Urinary Disorders				
Pollakiuria	20 (12%)	0	4 (2%)	0
Musculoskeletal Disorders				
Arthralgia	18 (11%)	0	2 (1%)	0

Injection site reactions, including discomfort/pain, erythema, hemorrhage, induration, urticaria, and warmth, were reported in 23 patients with no patients reporting a grade 3-4 event.

Comparison of the adverse event profile of Lutrate Depot 3 month with approved drugs found that hot flushes were reported in 77% of patients with Lutrate, 59% with Lupron 3 month, and in 56% with Eligard 3 month. Injection site transient burning and stinging was seen in 22% of patients receiving Eligard 3 month (pain in 3.5%) (b) (4)

Adverse Events of Concern

Low testosterone levels can result in a metabolic syndrome which affects glucose and cholesterol-triglyceride levels. (b) (4) In the study supporting the 3 month formulation, 52 patients had diabetes and 1 hyperglycemia. In this study, 9 (6%) patients had a laboratory report of grade 3-4 hyperglycemia. Hemoglobin A1c was not measured. No patient had a grade 3-4 cholesterol level.

An increase in arterial events has also been reported in large population-based studies of GnRH agonists. Single arm studies of this size and duration are unlikely to provide additional data. Arterial events, in both of the studies, included aortic aneurysm and myocardial infarction.

9. Advisory Committee Meeting

An Advisory Committee Meeting was not held.

10. Pediatrics

Since prostate cancer does not occur in children, a pediatric waiver has been granted.

11. Other Relevant Regulatory Issues

- Inspections:
  - The facilities inspection by the Office of Compliance is pending. Compliance is expected to recommend withhold following their facilities inspection of GP-Pharm S.A. See compliance review.
  - Inspections of the clinical sites and the central laboratory that conducted the testosterone assays were acceptable.

12. Labeling

Since the application did not meet its primary endpoints, product labeling was not initiated.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Complete Response
- Risk Benefit Assessment

Table 8: Risk-Benefit Summary and Assessment		
	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Although the requested indication is palliative treatment of advanced prostate cancer, GnRH agonists are used in patients with localized or metastatic prostate cancer. While a number of treatments are approved for use in prostate cancer, metastatic prostate cancer remains a lethal disease.	Metastatic prostate cancer is a lethal disease.
Current Treatment Options	A substantial number of GnRH agonists are currently approved for the treatment of prostate cancer.	While new treatments are needed for metastatic prostate cancer, Lutrate does not represent an improvement over existing therapy.
Benefit	(b) (4) Lutrate 3 month failed to demonstrate efficacy comparable to recently approved products. (b) (4) • Lutrate 3 month: 83.9% of patients achieved and	The percentage of patients who achieved and maintained castrate testosterone was lower than that of products recently approved. The clinical consequences for patients with non-castrate testosterone levels at the end of the dosing interval or who develop non-castrate levels as an acute-on-chronic effect are unknown.

	maintained castrate testosterone levels from Day 28-168	Given the substantial number of treatments available that are able to maintain castrate testosterone levels at these time points, Lutrate should not be approved.
Risk	The adverse event profile of Lutrate is comparable to other GnRH agonists. There were few grade 3 or serious adverse events and the adverse event profile is best characterized in terms of the common adverse events. (b) (4) [redacted] • Adverse events in ≥ 10% of patients receiving Lutrate 3 month include hot flush, fatigue/asthenia, injection site pain/discomfort, diarrhea, pollakiuria, and arthralgia.	The adverse event profiles of (b) (4) [redacted] Lutrate 3 month are acceptable.
Risk Management	Lutrate has not demonstrated adequate efficacy (see Benefit above).	Lutrate has not demonstrated an acceptable risk-benefit profile and a complete response letter will be sent.

- Recommendation for Postmarketing Risk Management Activities

Not applicable

- Recommendation for other Postmarketing Study Commitments

Not applicable

- Recommended Comments to Applicant

Please see complete response letter.

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/s/

VIRGINIA E MAHER
05/13/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	**205054**
Supporting document/s:	**4**
Applicant's letter date:	**07/29/2014**
CDER stamp date:	**07/31/2014**
Product:	**Lutrate Depot (b) (4) 22.5 mg)**
Indication:	**Lutrate® Depot (leuprolide acetate) is a gonadotropin-releasing hormone (GnRH) agonist indicated for palliative treatment of advanced prostate cancer.**
Listed Drug (Form 356h)	**Lupron Depot (FDA-approved)** (b) (4)
Applicant:	**GP Pharma SA**
Review Division:	**Division of Hematology Oncology Toxicology (Division of Oncology Products 1)**
Reviewer:	**Eias Zahalka, PhD, MBA**
Supervisor:	**Todd Palmby, PhD**
Division Director:	**John Leighton, PhD, DABT (DHOT-Acting) MD, (DOP1-Acting)**
Project Manager:	**Charlene Wheeler**

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205054 are owned by GP Pharma SA or are data for which GP Pharma SA has obtained a written right of reference. Any information or data

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1. Introduction

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin-releasing hormone (GnRH). This 505(b)(2) submission is for a new sustained-release formulation for Leuprolide acetate, Lutrate Depot. GP-Pharm SA has developed (b) (4) Lutrate Depot sustained-release (b) (4) ntended for the palliative treatment of patients with advanced prostate cancer. (b) (4) intended to be administered intramuscularly to the patient (b) (4) once every three months (Leuprolide Depot 22.5 mg).

For nonclinical support, the Applicant relies on the listed drug, Lupron Depot (Abbvie), which is marketed in the US (Form 356h).

(b) (4)

1.2 Brief Discussion of Nonclinical Findings

(b) (4)

(b) (4) original pharmacodynamic (PD) studies were conducted by the Applicant to assess testosterone suppression levels in dogs (a marker of activity) following single intramuscular administration of Lutrate Depot (b) (4) 22.5 mg. (b) (4) Castrate levels following Lutrate Depot administration were achieved between Days 7 to 21, and testosterone levels remained low until study termination. (b) (4)

In addition to reliance on the listed drug, the Applicant provided published safety data to further characterize the safety profile of Leuprolide acetate. These safety data were considered supportive/supplemental.

The Lutrate Depot formulation contains an excipient, triethyl citrate (TEC), that was not previously characterized when administered by the intramuscular route. TEC is listed in the FDA Inactive Ingredients Search for Approved Drug Products and is contained at a maximum potency up to (b) (4) mg in an oral, delayed-action tablet. The safety profile of intramuscularly administered TEC was therefore characterized in a single- /repeat-dose (28-day) toxicology study in rats at doses which exceed that expected clinically. No adverse toxicity was reported in the TEC-treated animals. Based on this data and previous experience in approved drugs containing TEC for oral administration, this

excipient was considered qualified at the specified level for intramuscular injection in Lutrate Depot.

The Lutrate Depot drug product contains the same active pharmaceutical ingredient, leuprolide acetate, as the listed drug formulated in the same or lower strength. There are no safety concerns with the excipients in the Leutrate Depot drug product. Nonclinical PK/PD studies in dogs demonstrated that the Lutrate Depot intramuscular administration resulted in exposures and testosterone responses as would be expected for the listed drug and comparable to Procrin®, a leuprolide acetate depot product approved in Europe. In addition, results from clinical trials conducted with Lutrate Depot do not indicate that there are any significant safety signals that would suggest additional nonclinical studies are needed. These combined data provide an adequate scientific bridge for reliance on the listed drug, Lupron Depot, for the nonclinical requirements for approval as a 505(b)(2) NDA. Since FDA's previous finding of safety and efficacy is captured in the product labeling and includes findings inferred from fact of approval, no further nonclinical studies are needed to support the approval of Lutrate Depot.

1.2 Recommendations

1.2.1 Approvability

There are no issues from the Pharmacology/Toxicology discipline that would preclude approval of Lutrate Depot (b) (4) 22.5 mg) for the proposed indications.

2. Drug Formulation

Lutrate Depot (proposed tradename for Leuprolide Depot)
(b) (4)

- Lutrate Depot 22.5 mg once per three months.

Generic Name: Leuprolide Depot, Leuprolide

In the formulations, Leuprolide acetate (the API) is entrapped inside microspheres formed by a biodegradable polymer (b) (4) PLA for Lutrate Depot 22.5 mg) and triethylcitrate. (b) (4)

The product, as described by the applicant, consists of a vial containing the powder, a prefilled syringe containing the solvent necessary for powder reconstitution (mannitol 0.8% solution), and a device used for connecting the syringe directly onto the vial; thereby allowing a direct reconstitution of the powder and injection of the reconstituted product to patient.

TABLE 1 - Product Formula

INGREDIENT	QUANTITY	FUNCTION	REFERENCE TO STANDARDS
	(b) (4) LUTRATE 22.5 mg		
Active Ingredient			
Leuprolide Acetate[2]	22.5 mg	Active Ingredient	Ph Eur*
Excipients			
[redacted]	(b) (4)	(b) (4)	In - House
PLA	(b) (4)		In - House
Triethyl citrate (TEC)			Ph Eur/USP*
Mannitol	88.4 mg		Ph Eur/USP*
Carmellose Sodium	25.0 mg		Ph Eur/USP*
Polysorbate 80	3.8 mg		Ph Eur/NF*

* Current Edition

(excerpted from Applicant's report)

3. Pharmacological Class

GnRH agonist

4. Mechanism of Action (as listed in the proposed label)

Leuprolide acetate has GnRH agonist [redacted] (b) (4) This effect is reversible upon discontinuation of drug therapy.

In humans, (b) (4) administration of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in premenopausal females). [redacted] (b) (4)

5. Nonclinical Activity

The Applicant conducted an original nonclinical bridging study to provide an adequate scientific basis for reliance upon the listed drug (Lupron Depot®). A pharmacokinetic (PK) and pharmacodynamic (PD) bioequivalence study of Lutrate Depot versus the marketed drug *Procrin* Depot® (European trademark of listed drug, Lupron Depot®) was conducted. [redacted] (b) (4)

A bridging study for the three-month formulation (Lutrate Depot 22.5 mg) was not conducted by the Applicant. The Applicant provides the following justification:

(b) (4)

Additionally, the PK/PD profile of Lutrate Depot was studied in animals, using testosterone as a marker of activity, and these data were submitted to provide a qualitative bridge to the three-month (22.5 mg) Lutrate Depot formulation.

5.1 Original Studies Submitted[2]

Study #	Study Title	Reviewed	
		Full	Summarized
Pharmacodynamic			
s34055	Leuprolide acetate 22.5 mg Depot GP-Pharm (Lot # 10603-1). Testosterone Profile in Beagle Dogs Following a Single Dose Intramuscular Administration of Slow Release Leuprolide Formulation	X	
s32312	Leuprolide acetate 22.5 mg Depot GP-Pharm (Lot # 10311-1). Testosterone Profile in Beagle Dogs Following a Single Dose Intramuscular Administration of Slow Release Leuprolide Formulation	X	
(b) (4)			

[1] *[bracketed italicized text was added by reviewer to clarify the Applicant's statement]*

[2] Additional published data were provided to supplement pivotal data, and these are provided in Appendix 1.

			(b) (4)
IQ13-00180-PD	Testosterone profile in beagle dogs following a single dose intramuscular administration of slow release Leuprolide formulation.		Not Reviewed
GPLP3M-VAL14001	Validation of the Beagle dog model to predict efficacy of Leuprolide depot formulations in humans		Not Reviewed
CD059817FC	Testosterone profile in beagle dogs following single dose intramuscular administration of Leuprolide		Not Reviewed
Pharmacokinetic			
CRO-01-30	Leuprolide: Pharmacokinetic and pharmacodynamic bioequivalence of a new microcapsule Leuprolide 7.5 mg formulation versus Procrin® 7.5 mg (Abbott) in the beagle dog following intramuscular administration	X	
s13-087	Leuprolide levels determination by RIA in dog plasma from PK/PD study IQ13-00180 (method development)		Not Reviewed
RA-284	Determination of Leuprolide in dog plasma samples by RIA		Not Reviewed
GP-IP3M-PK	Leuprolide profile in beagle dogs following a single dose intramuscular administration of slow release leuprolide formulation	X	
UA037	Determination of leuprolide in dog plasma samples by RIA		Not Reviewed
Toxicology Studies			
s27520	28-Day Intramuscular Toxicity Study in the Rat for Triethyl Citrate (excipient in the Leuprolide Depot)	X	
FCIL005FT	Local toxicity study (28 days) after single intramuscular administration in the rabbit of Placebo vLP1m		Not Reviewed
FCI0812FT	28 Days Intravenous Toxicity Study In The Rat for Docetaxel-Patented GP-Pharm Formulation Vehicle		Not Reviewed
IQ13-00180	Leuprolide acetate 22.5 mg Depot GP-Pharm. PK/PD study of leuprolide in Beagle dogs following a single dose IM administration of Slow Release Leuprolide		Not Reviewed

	Formulation. Administration and blood extraction.		

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Study title: Leuprolide acetate 22.5 mg Depot GP-Pharm. Testosterone Profile in Beagle Dogs Following a Single Dose Intramuscular Administration of Slow Release Leuprolide Formulation	
Study no.:	s34055 and s32312
Objective:	To investigate the activity of two lots of Leuprolide acetate 22.5 mg depot GP-Pharm (10603-1 and 10311-1) in the suppression of plasma testosterone levels in Beagle dogs
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Was not provided
Experimental starting Date:	6 July, 2011
GLP compliance and QA statement:	Yes (OECD)
Drug and lot #:	Leuprolide acetate 22.5 mg depot; 10603-1 and 10311-1 (the clinical batch).

Methods:	
Doses/ Number/Sex/Group:	1.186 mg/kg; 4-6 males/ one Group
Route/Frequency of dosing:	Intramuscularly (i.m.; rear leg); single dose
Dose volume:	0.1054 mL/kg
Formulation/Vehicle:	The powder contained in the test article vial was reconstituted with 2 mL of 0.8% Mannitol solution
Species/Strain:	Beagle dogs
Age:	2 -5 years
Weight:	11.64-18.02 kg
End points evaluated:	• Clinical observations (frequency of observations was not listed in the report) • Testosterone level: Pre-dose (Day 0), 3 and 6 hours post-dose, 1, 2, 3, 4, 14, 21, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154 and 168 days post-dose. Blood was collected between 8-11 am except on dosing day. Plasma Leuprolide levels were determined using an RIA kit.
Deviation from study protocol:	None of the deviations affected the integrity or interpretability of the study.

Results:

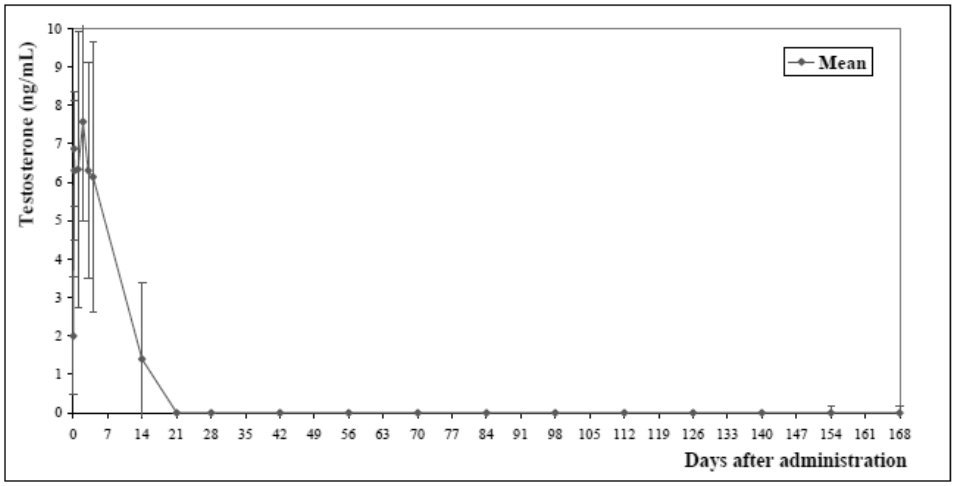
- The Applicant stated that there were no clinical observations reported. Individual data were not provided by the Applicant in this report, so this reviewer could not confirm the conclusions.
- Testosterone levels were quantifiable 3 hours postdose through Day 14. Levels gradually declined following Day 4, and by Day 21 levels were unquantifiable or were lower than the pre-dose levels (≤0.37 ng/mL for Lot #10603-1, or ≤0.99

ng/mL for Lot # 10311-1). Testosterone levels continue to be unquantifiable through Day 140 (Lot # 10311-1) or Day 168 (Lot # 10603-1), although testosterone levels for Lot # 10311-1 were quantifiable again by Day 154.

Reviewer note
Castration levels of testosterone in humans were 50 ng/dl (or 0.5 ng/mL).

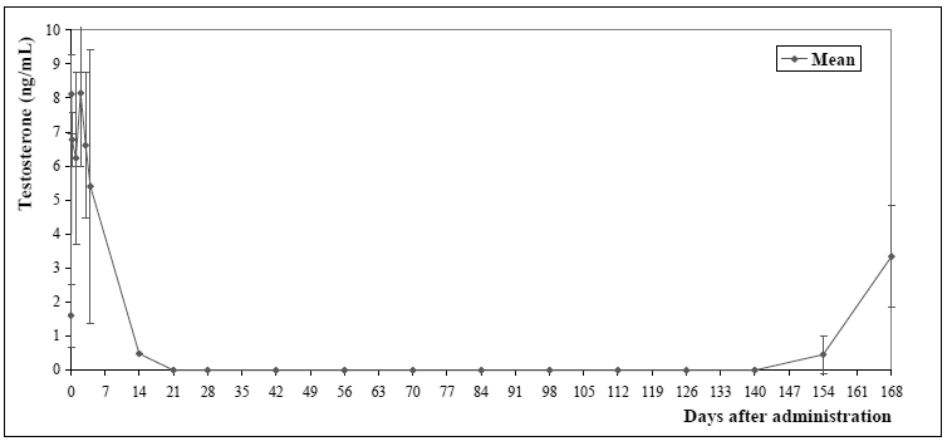
TESTOSTERONE LEVELS IN DOG PLASMA SAMPLES (ng/mL)
Mean levels

Leuprolide acetate 22.5 mg Depot GP-Pharm 10603-1
Intramuscular administration



TESTOSTERONE LEVELS IN DOG PLASMA SAMPLES (ng/mL)
Mean levels

Leuprolide acetate 22.5 mg Depot GP-Pharm 10311-1
Intramuscular administration



(excerpted from Applicant's report)

Conclusion

The observed Leuprolide acetate 22.5 mg Depot PD (testosterone) profiles in the two tested batches were very similar; with an initial peak of plasma testosterone levels

followed by a gradual decline. Low levels were maintained until Day 140 or 168. This pattern of testosterone suppression following a single dose of Leuprolide acetate (22.5 mg) (b) (4)

(b) (4)

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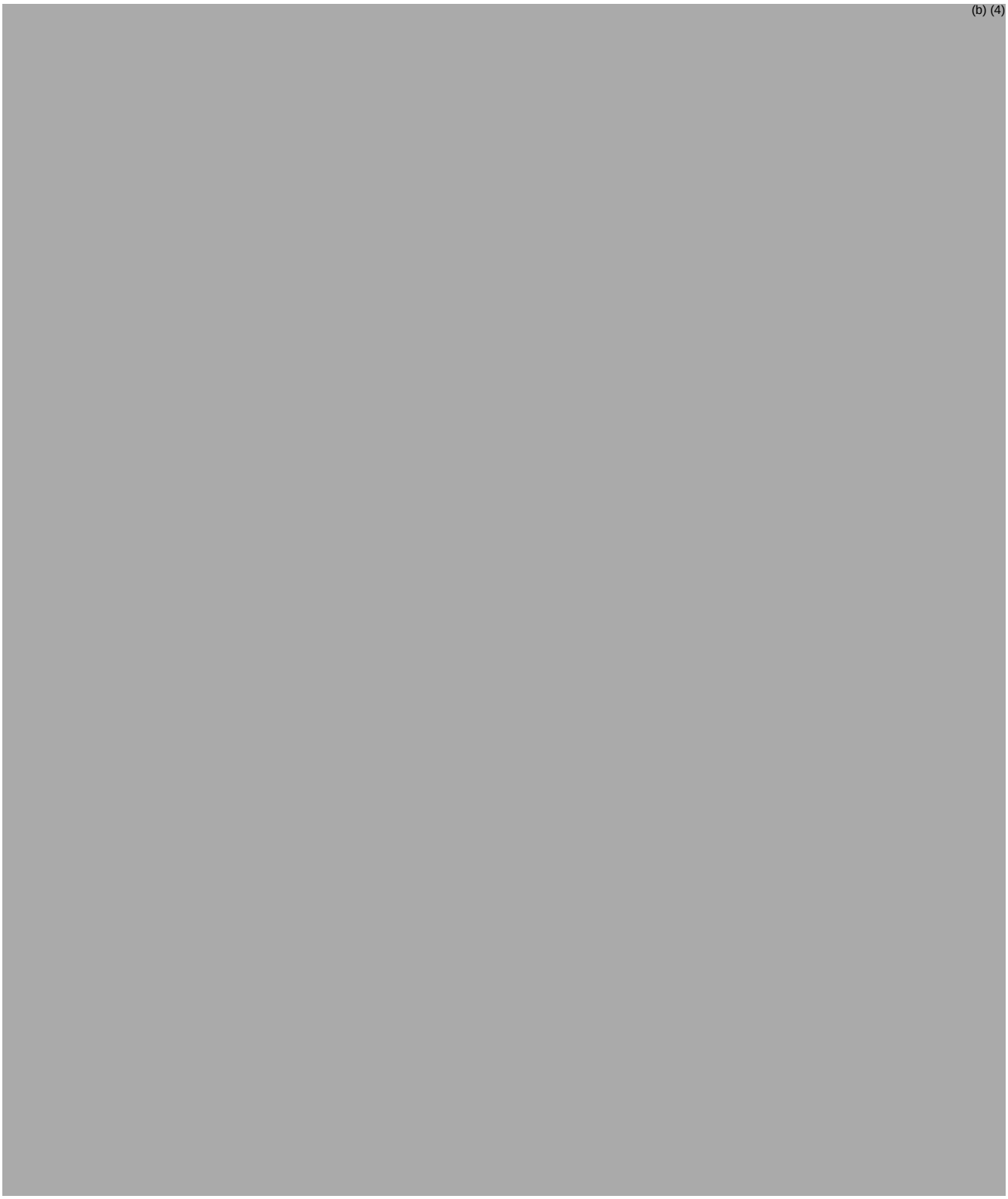
(b) (4)



8. Pharmacokinetics

Study #: GP-LP3M-PK	**Title:** Leuprolide profile in beagle dogs following a single dose intramuscular administration of slow release leuprolide formulation **GLP:** Yes

Objectives: To evaluate leuprolide pharmacokinetic profile in dog obtained after administration of the clinical batch (10311-1), the clinical back-up batch (10603-1) and other validation batches (21022-1, 21108-1, 21111-1), in three different preclinical studies (S32312, S34055 and IQ13-00180).

Methods:
Four (S32312), 6 (S34055) and 9 (IQ13-00180) dogs were administered Leuprolide acetate 22.5 mg depot GP-Pharm (batches 10311-1, 10603-1, 21022-1, 21108-1, 21111-1) intramuscularly at the dose of 1.186 mg/kg of Leuprolide acetate and a volume of 0.1054 mL/kg. Blood samples were collected at the following times: Pre-dose (day 0), 3 and 6 hours, 1, 2, 3, 4, 14, 21, 28, 42, 56, 70, 84, 98, 112 (last day for the validation batches), 126, 140, 154 and 168 (last day for the clinical batches) days post-dose. Plasma Leuprolide levels were determined using a RIA kit.

Results:
Batches 10311-1 and 10603-1

After dose administration, Leuprolide levels peaked followed by a decline in levels reaching values of approximately 1000 pg/mL by Day 21. These levels were maintained until Day 98, at which time Leuprolide concentrations started to gradually decrease, and were unquantifiable by Day 168.

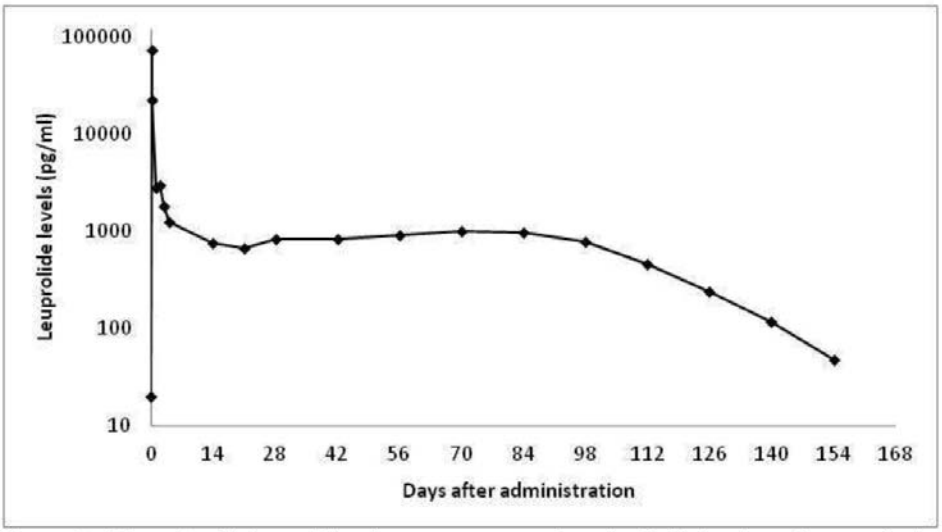


Figure 2: Mean (n=4) leuprolide plasma concentrations (pg/mL) in dog after a single intramuscular administration of Leuprolide acetate 22.5 mg Depot GP-Pharm, batch 10311. *Values < LLOQ were assigned ½ LLOQ for plotting the pharmacokinetic profile. If the calculated mean value was less than LLOQ, then that time point was ignored for plotting the mean pharmacokinetic profile.*
(excerpted from Applicant's report)

Batch 10603-1

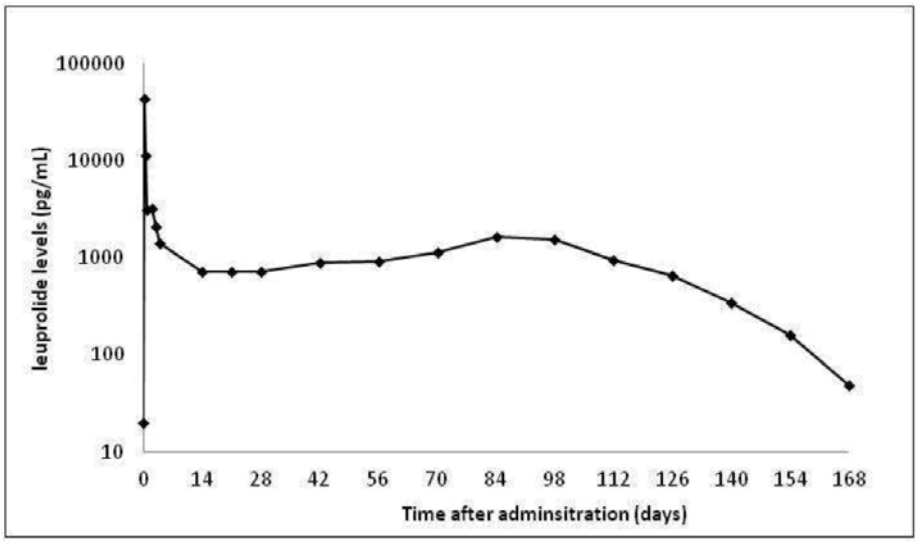


Figure 4: Mean (n=6) leuprolide plasma concentrations (pg/mL) in dog after a single intramuscular administration of Leuprolide acetate 22.5 mg Depot GP-Pharm, batch 10603-1 *Values < LLOQ were assigned ½ LLOQ for plotting the pharmacokinetic profile. If the calculated mean value was less than LLOQ, then that time point was ignored for plotting the mean pharmacokinetic profile.*

(excerpted from Applicant's report)

Batches 21022-1, 21108-1, 21111-1

After dose administration Leuprolide levels peaked followed by a decline in levels reaching values of approximately 1000 pg/mL by Day 21. These levels were maintained until day 112.

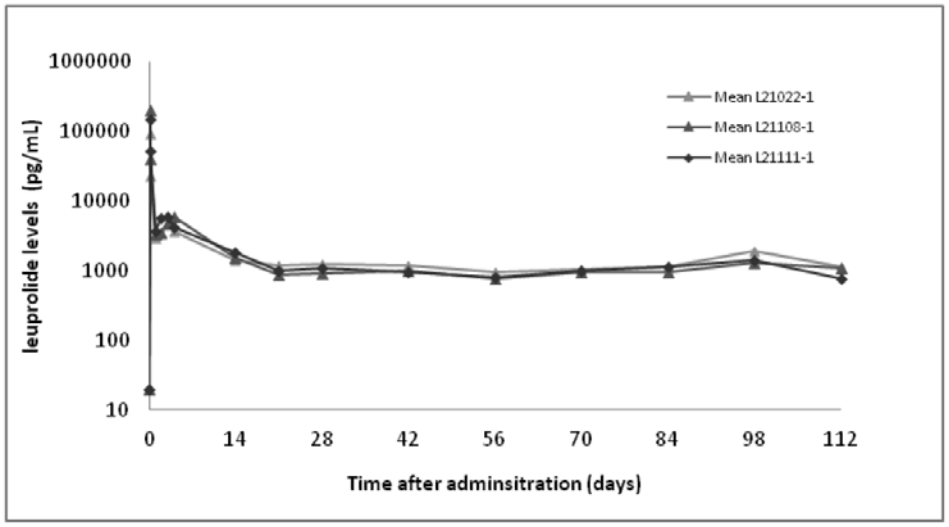


Figure 11: Comparison of mean (n=3) leuprolide plasma concentrations (pg/mL) in dog after a single intramuscular administration of Leuprolide acetate 22.5 mg Depot GP-Pharm for batches 21022-1, 21108-1 and 21111-1, respectively. *Values < LLOQ were assigned ½ LLOQ for plotting the pharmacokinetic profile. If the calculated mean value was less than LLOQ, then that time point was ignored for plotting the mean pharmacokinetic profile.*

(excerpted from Applicant's report)

9. General Toxicology

9.1 Repeat-Dose Toxicity

It was stated by the Applicant that all the excipients in Leuprolide Depot are known and well characterized substances and already used in other injectable drug formulations including the listed drug, Lupron Depot® with the exception of triethylcitrate (TEC). The toxicity profile of TEC was evaluated by the applicant in a 28-Day intramuscular toxicity study in rats.

Study title: 28-Day Intramuscular Toxicity Study in the Rat for Triethyl Citrate (excipient in the Leuprolide Depot)	
Study no.:	s27520
Objectives:	• To evaluate the cumulative toxicity of Triethyl Citrate after daily intramuscular administration to rats for a period of 28 days at a single dose level. • The acute toxicity of Triethyl Citrate was evaluated when administered by intramuscular route to rats at two dose levels, followed by an observation period of 27 days.
Sponsor:	GP-Pharm S.A.
Conducting laboratory and location:	(b) (4)
Experimental Starting Date:	17 May, 2010
GLP compliance/QA statement:	Yes (OECD)
Drug and lot #:	Triethyl Citrate (Pharmaceutical excipient); Lot # M04e101, M04e102, M04e103.

Methods:

Doses/ Number/Sex/Group:	<table><tr><th>Groups</th><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th></tr><tr><th>Test Item</th><th>-</th><th>Triethyl Citrate</th><th>-</th><th>Triethyl Citrate</th><th>Triethyl Citrate</th></tr><tr><th>Dose Levels</th><th>0 mg/kg/day*</th><th>0.017 mg/kg/day</th><th>0 mg/kg *</th><th>0.48 mg/kg</th><th>2.40 mg/kg</th></tr><tr><td>Males A</td><td>1-10</td><td>11-20</td><td>-</td><td>-</td><td>-</td></tr><tr><td>Males B</td><td>-</td><td>-</td><td>41-45</td><td>46-50</td><td>51-55</td></tr><tr><td>Females A</td><td>21-30</td><td>31-40</td><td></td><td>-</td><td>-</td></tr><tr><td>Females B</td><td>-</td><td>-</td><td>56-60</td><td>61-65</td><td>66-70</td></tr></table> A: Animals for toxicity testing, daily administration (28 days) B: Animals for toxicity testing, once administration (day 1) *: Control animals were treated with water for injection only.
Route and frequency:	Intramuscular injection; once daily for 28 days (Groups 1 and 2) **and** single dose (Groups 3 - 5)
Dose volume:	0.15 mL/kg (Groups 1 and 2) and 0.25mL/kg (Groups 3 - 5)
Formulation/Vehicle:	The test article was supplied as a solution ready to use at three concentrations (0.11, 1.9 and 9.68 mg/mL)
Sex/Species/Strain:	Male and female WIST rats
Age/Weight:	5-7 weeks (males) and 6-9 weeks (females); 155-193 g (males) and 130-152 g (females)
Endpoints evaluated:	Mortalities, clinical signs, body weight, food consumption, ophthalmology, hematology, coagulation, chemistry, urinalysis, organ weights, macroscopic and microscopic evaluations (all groups). Histopathology peer review was not conducted.
Deviation from study protocol:	None of the deviations affected the integrity or interpretability of the study.

Results:

Mortalities
There were no mortalities reported by the Applicant.

Clinical Observations
There were no test article-related clinical observations reported by the Applicant.

Reviewer comment
The Applicant did not provide the individual data for the clinical observations.

Body Weight and food consumption

There were no adverse test article-related effects on mean body weights, body weight gains and food consumption.

Ophthalmology: No test article-related ophthalmic findings were reported.

Hematology, Clinical Chemistry and Urinalysis

No test article-related clinical pathology (hematological, clinical chemistry and urinalysis) findings were reported.

Macroscopic Findings

There were no test article-related findings reported.
The only finding that was reported at 0.017 mg/kg/day included discolored ovaries and uterus. However, the effects were not correlated with microscopic findings.

Organ Weights
There were no test article-related findings reported.

Increases in a number of relative organ weights were reported at 0.017 mg/kg/day. Higher absolute and relative weights were reported in the pituitary of males and females and in the lungs, liver, kidneys and spleen of females. The effects were not correlated with microscopic findings.

Microscopic Findings
There were no test article-related microscopic findings reported.

Conclusion
There were no adverse test article-related effects reported after single (2.48 mg/kg) or repeat dose for 28-day (0.017 mg/kg/day) intramuscular dose of triethyl citrate to rats. The TEC level in the rat single-dose arm of the study was 2.48 mg/kg (or HED of 24.12 mg) which is higher than the 17.4 mg TEC level specified in the maximum clinical formulation dose (22.5 mg). As such, the excipients triethyl citrate (TEC) in Lutrate Depot is considered qualified at the specified levels for intramuscular injection.

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/s/

EIAS A ZAHALKA
04/27/2015

TODD R PALMBY
04/27/2015

Clinical and Statistical Reviews

Application Type	NDA
Submission Number	205054
Submission Code	None
Letter Date	July 31, 2014
PDUFA Goal Date	May 31, 2015
Clinical Reviewer	Yangmin M Ning, M.D., Ph.D.
CDTL	V. Ellen Maher, M.D.
Statistical Reviewer	Hui Zhang, Ph.D.
Statistical TL	Shenghui Tang, Ph.D.
Review Completion Date	April 20, 2015
Established Name	Leuprolide Acetate
Proposed Trade Name	LUTRATE
Therapeutic Class	Gonadotropin releasing hormone receptor agonist
Applicant	GP-Pharm S.A
Priority Designation	Standard Review

Formulation: Suspension for intramuscular injection

Dosing Regimen: (b) (4) *LUTRATE DEPOT 22.5 mg administered every 12 weeks"*

Proposed Indication: Palliative treatment of advanced prostate cancer

Intended Population: Adults with prostate cancer

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Commonly Used Abbreviations in the Review

Abbreviation	**Full Term**
ADT	Androgen Deprivation Therapy
AE	Adverse Event
CRF	Case Report Form
ECG	Electrocardiogram
PP	Per Protocol
GnRH	Gonadotropin Releasing Hormone
ITT	Intent-to-Treat
PSA	Prostate Specific Antigen
PK	Pharmacokinetics
SAE	Serious Adverse Event
TEAE	Treatment-Emergent Adverse Event
TRAE	Treatment-Related Adverse Event

1. Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This combined clinical and statistical review of NDA 205054 for Lutrate (b) (4) 22.5 mg reveals inadequate evidence to support the proposed use (b) (4) and, therefore, recommends that this NDA not be approved.

Additional clinical studies with acceptable quality Lutrate formulations should be conducted to demonstrate the effectiveness (b) (4) in patients with advanced prostate cancer.

1.2 Risk Benefit Analysis

The benefit risk analysis of this NDA was based on the review findings from clinical studies conducted (b) (4) in patients with prostate cancer. (b) (4) Study GP/C/05/PRO for Lutrate 22.5 mg. (b) (4) was designed to investigate the efficacy and safety of the (b) (4) formulation. The primary endpoint (b) (4) was the proportion of patients who achieved (at Day 28) and maintained castrate levels of testosterone from Day 28 through Day 168 (See Section 5.3 for details). Determination of castration in each study patient was based on blood testosterone levels measured in a central laboratory.

(b) (4)

Study GP/C/05/PRO had 163 patients enrolled, with 162 evaluable for assessment of the primary endpoint. Eleven percent of the enrolled patients had metastatic prostate cancer. By Day 28, castration was achieved in 96.9% (95% CI: 92.9%; 99.0%) of the evaluable patients. From Day 28 through Day 156, castration was maintained in 83.9% (95% CI: 77.3%, 88.8%) of the evaluable patients. This castration maintenance rate was also based on a Kaplan-Meier analysis in which detected testosterone surges and missing data were addressed. The results showed that Lutrate 22.5 mg was not efficacious in maintaining castration in this study either. To be efficacious, study drug should maintain castrate testosterone levels in a sufficient number of patients to ensure that the lower bound of the 95% confidence interval is ≥ 87%.

The commonly observed adverse events (b) (4) were hot flushes, arthralgia, fatigue, injection site pain or discomfort, headache, and diarrhea. The majority of the adverse events were mild or moderate (b) (4) Grade 1-2 in Study GP/C/05/PRO. Important laboratory abnormalities were hyperglycemia, increases in hepatic transaminases and serum creatinine. The majority of the abnormalities were Grade 1-2. Severe hyperglycemia (Grade 3 or 4) was found in approximately 6% of patients in each study. The observed adverse events and laboratory abnormalities were consistent with the known safety profile of other GnRH analogs.

(b) (4) were not efficacious in maintaining castration during an approximately 5-month maintenance period. This was due primarily to a large number of testosterone surges that were detected after a repeat dose. Given the (b) (4) % overfill of study product in the clinical batches and the questionable dose uniformity in their manufacturing (Section 4.1), the detected testosterone surges may reflect issues concerning the product quality and/or leuprolide release equilibrium and efficiency from the suspension depots. Because of the CMC issues (Section 4.1), the reviewers are concerned about the interpretability of clinical data and/or the reliability of the analyses based on the submitted data. The inadequacy of castration maintenance as shown in the study (b) (4) may not be simply by chance, but likely relates to the quality of each study product. Overall, the benefit (b) (4) could not be unvaryingly established with the submitted data. Additional clinical studies are needed should the identified CMC issues be addressed satisfactorily.

1.3 Recommendations for Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations on Post Marketing Requirements/Phase 4 Commitments

None

2 Introduction and Regulatory Background

2.1 Product Information

Lutrate Depot is a new microsphere formulation of leuprolide acetate, manufactured by the applicant. In this NDA, (b) (4) 22.5 mg for 3-month administration.

(b) (4)

Each vial of Lutrate Depot 22.5 mg was designed to deliver leuprolide acetate (22.5 mg), PLA (b) (4) triethylcitrate (TEC) (b) (4) polysorbate 80 (3.8 mg), mannitol (88.4 mg) and carmellose sodium (25 mg).

(b) (4) each vial is accompanied by a prefilled syringe and a transfer device containing a sterile needle. The prefilled syringe contains the reconstitution diluent, including mannitol (16 mg), water for injections USP, and sodium hydroxide and hydrochloric acid USP to control pH.

Reviewer's Comments:
(b) (4) *the true quantity of leuprolide acetate contained in each vial is higher than the target dose as specified in the above product description. See Section 4.1 regarding the CMC concerns* (b) (4) *% overfill for the 22.5 mg formulation. The overfill also occurred in the clinical batches that were used in the* (b) (4) *clinical studies* (b) (4) *Study GP/C/05/PRO for Lutrate 22.5 mg).*

2.2 Tables of Currently Available Treatments for Proposed Indications

A number of GnRH analogs that have the same indication are available in the USA. Table 1 lists these analogs.

Table 1: FDA-Approved GnRH Analogs for Use in Patients with Advanced Prostate Cancer

Class	Product Name	Year of Initial Approval
GnRH Receptor Agonist*	Leuprolide**	1985
	Goserelin	1989
	Triptorelin	2000
	Histrelin	2004
GnRH Receptor Antagonist	Degarelix	2008

** Products may have different formulations or delivery systems to achieve longer drug action (e.g., administered every 3, 4, 6 or 12 months).*

*** Including leuprolide-based products approved under 505 (b) (2) such as Eligard.*

2.3 Availability of Proposed Active Ingredient in the United States

Leuprolide acetate has been available since 1985. It is marketed under two brand names: Lupron and Eligard. (b) (4) leuprolide acetate 7.5 mg is approved for monthly administration and leuprolide 22.5 mg for administration every 3 months. (b) (4)

2.4 Important Safety Issues with Consideration to Related Drugs

In January of 2011, all GnRH receptor agonists indicated for the treatment of prostate cancer had the following labeling added to their Warnings and Precautions:

- Hyperglycemia and Diabetes: Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH analogs. Monitor blood glucose level and manage according to current clinical practice.

- Cardiovascular Diseases: Increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH analogs in men. Monitor for cardiovascular disease and manage according to current clinical practice

Recently, the following warning was added to all GnRH analogs as another labeling change.

- Effect on QT/QTc Interval: Androgen deprivation therapy may prolong the QT interval. Consider risks and benefits.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Key pre-submission regulatory activities related to this NDA are summarized in Table 2.

Table 2: Key Regulatory Activities for the GP- Pharm Leuprolide Acetate Clinical Development

Milestone	Date	Clinical Comments
[redacted] (b) (4)		
Study GP/C/05/PRO for Lutrate (leuprolide acetate 22.5 mg) conducted	07/2011 -07/2014	A single-arm study of Lutrate 22.5 mg (leuprolide acetate 22.5 mg) in patients with histologically proven carcinoma of the prostate. For its efficacy claim, the statistical plan assumed that at least 93% of patients maintained castration.

(b) (4)		
Submission of NDA 205054 for Lutrate (Leuprolide Acetate (b) (4) 22.5 mg)	07/31/2014	The NDA received "Standard" review.

2.6 Other Relevant Background Information

Androgen deprivation therapy remains the cornerstone of treatment for patients with metastatic prostate cancer. It can be achieved either surgically with bilateral orchiectomy or biochemically with drugs. The goal is to eliminate or persistently suppress the testicular synthesis of testosterone. Since leuprolide acetate was approved in 1985, use of a GnRH analog has become the most common approach to attain androgen deprivation.

Evaluation of the effectiveness of GnRH analogs has been based on their ability to achieve and maintain castration levels of testosterone (≤ 0.5 ng/mL), a surrogate endpoint that has been used for nearly two decades[1]. For almost all approved GnRH receptor agonists, ≥90% of patients achieved and maintained castration from Day 28 to the study end. To assure the effectiveness of a GnRH analog, a lower 95% CI boundary of at least 87% of castration maintenance has been required since the regulation of GnRH analogs in prostate cancer was transferred to the Office of Hematology Oncology Products (OHOP). This requirement was implemented in the evaluation and approval of three new GnRH analog formulations by OHOP[2] (Table 3). Note that in the approval of degarelix, the requirement for the lower 95% CI boundary was at least 90%.

Table 3: Key Findings from Studies Supporting the Approvals of GnRH Analogs Since 2008

1 Fourcroy J. Regulatory history of hormone therapy for prostate cancer. Mol Urol. 1998; 2:215–220
2 Clinical reviews of the three products are available at drugs@fda.

GnRH Product (Approval Year)	**Sampling time points for testosterone after Day 28**	**Inclusion of all available data***	**Castration maintenance** (95% CI)	**Analysis with the K-M method** (N)
Lupron (leuprolide) 45 mg q 6 mos (2011)	Every 4 weeks and 2, 4, 8 hours after the second dose, followed by Days 1, 2, 7 and 14 thereafter	Yes	93.4% (89.2, 97.6) from Day 28 through 337	Yes (N=148)
Trelstar (triptorelin) 22.5 mg q 6 mos (2009)	Every 4 weeks and Day 3 after the second dose (in 50% of the patients)	Yes	93.5% (88.7, 99.8) From Day 57-337	Yes (N=120)
Degarelix 240 mg followed by 80 mg q 1 mo (2008)	Every 4 weeks after each monthly dose	Yes	97.2% (93.5, 98.8) Day 28-364	Yes (N=207)

**Including testosterone surges that were treated as maintenance failures in the Kaplan-Meier (K-M) analysis.*

For each product's castration maintenance rate, its lower bound of the 95% CI is shown in red.

To reliably assess the rate of castration maintenance, testosterone surges (>0.5 ng/mL) detected throughout a study have been considered as treatment failures in the evaluation of GnRH analogs. This is particularly important for GnRH receptor agonists since these products attain castration by desensitizing the pituitary gland. A testosterone surge after Day 28 or after a repeat dose suggests that the gland may not have been sufficiently desensitized, but rather, remained sensitive to their agonistic stimulation.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality and integrity of the submitted datasets were found to be adequate for this review. The submitted analysis datasets were in a "Listing form". There were no "dataset definition" files for the tabulation datasets (b) (4) in the initial submission. (b) (4) These issues along with others such as protocol deviations were conveyed to the applicant and were addressed acceptably.

(b) (4) study reports considered how to handle missing testosterone data at key time points if the missing data was unrelated to study treatment, and excluded testosterone surges after a repeat dose from the primary endpoint analyses. This made interpretation of the applicant's efficacy analyses challenging. For instance, determination of whether a missing testosterone value was unrelated to study treatment can be very difficult in open-label single-arm studies.

In addition, there were numerous issues regarding the CMC process and drug specifications. See the final CMC review.

3.2 Compliance with Good Clinical Practices

Three clinic study sites (Table 4) were selected for inspections conducted by the Office of Scientific Investigation (OSI). Approximately 70% of patients enrolled in the two studies were from United States, making the conduct of domestic only inspections reasonable. The three selected sites had a large number of patients, accounting for 35% of the total patients from the USA. One site in South Carolina enrolled 18% of the patients for the two studies.

Based on the OSI inspection summary dated March 11, 2015, the data from the three sites appear clinically reliable for the two studies. The classification for clinical investigators Dr. Karlin and Dr. Shore (preliminary) is No Action Indicated (NAI), whereas the classification for clinical investigator Dr. Belkoff is Voluntary Action Indicated (VAI) since a number of minor record keeping issues were identified from the inspection. For example, *"a hot flash adverse event starting* (b) (6) *for Subject* (b) (6)*, was evaluated as probably/likely related to the test article, but was reported to the sponsor in the eCRF as not related"*. The identified issues appear to be isolated for Dr. Belkoff's site and should not importantly impact the overall study safety assessment.

For details, see final DSI clinical inspection reports on the 3 sites.

Table 4: Study Sites Selected for Inspection

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication/Primary endpoint and other endpoints for verification
(b) (4)			
Site 1 Dr. Neal Shore Carolina Urologic Research Center. 823 82nd Parkway, Suite B. Myrtle Beach South Carolina, 29572 Tel: 843-449-1010; Fax: 843-286-0119 e-mail: nshore@gsuro.com	GP/C/05/PRO**	24	Blood sampling for serum testosterone Protocol violations and reporting of adverse reactions
Site 24 Dr. Laurence Belkoff Urologic Consultants at SE PA 1 Presidential Blvd, Suite 100 Bala Cynwyd Pennsylvania, 19004 Tel: +6106670458; Fax: +6106681548	GP/C/05/PRO**	27	Blood sampling for serum testosterone Protocol violations and reporting of adverse reactions
(b) (4)			

**GP/C/05/PRO: "*Efficacy and Safety of a New Leuprolide Acetate 22.5 mg Depot Formulation in the Treatment of Prostate Cancer*"

The two study titles were based on the Applicant's original protocols.

In addition, the clinical pharmacology review team requested for an inspection of the bioanalytical site where samples from (b) (4) GP/C/05/PRO were analyzed for central determination of testosterone levels. This is important to assure that the quality of testosterone data as submitted is acceptable for efficacy analyses. Currently, results of this inspection are pending. Please see the final clinical pharmacology review regarding the inspection and its recommendation.

3.3 Financial Disclosures

An FDA Form 3454 was submitted to certify the financial interests and arrangement of the investigators involved in (b) (4) Study GP/C/05/PRO. In the form, Antonio Parente Duefia, Chairman of GP-Pharm S.A, certified that all the investigators had no financial conflict of interest based on their disclosed information.

Since a central laboratory was used to analyze serum testosterone levels, the investigator's financial conflicts of interest, if any, were less likely to affect the efficacy assessment of castration achievement and maintenance in the two studies.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC review team identified the following key issues about the quality of (b) (4) Lutrate (b) (4). These were based on the recent CMC review findings. See the final CMC review and risk assessment of these issues along with other deficiencies.

"The amount of overfilling (b) (4) with (b) (4) 22.5 mg, appears to be significantly larger than the requirement stated in USP <1151> "slight excess to the labeled size or the volume that is to be withdrawn". In addition, the amount of excipients used in the formulation, such as (b) (4) will vary (b) (4). An overage, (b) (4) 22.5 mg formulation is noted when fill in vial. The Dose Uniformity appears to not be accurately controlled throughout manufactured batch of the product according to USP<905>".

"The overfilling and overage used (b) (4) will affect the quality of final "intended use" with regard to dosage strength and purity".

4.2 Recommendation from the Office of Compliance

The OC's recommendation is classified as "Official Action Indicated" or to withhold this NDA. The recommendation is based on the findings of a routine pre-approval inspection. Total 11 verbal issues were conveyed to the applicant. Of them, the following are of particular concern to the clinical evaluations of the two formulations intended for marketing in the USA.

(b) (4)

See the final OC review of the inspection findings and its recommendation.

4.3 Product Proprietary Name

The applicant's proposed proprietary name, Lutrate Depot, for its leuprolide (b) (4) 22.5 mg (b) (4) was reviewed by the Division of Medication Error Prevention and Analysis and found acceptable.

4.4 Clinical Pharmacology

The clinical pharmacology review team specified that based on the recent communication, there were no issues identified from the OSI bioanalytical assay inspection. The inspection report is expected to be available soon.

See details in the clinical pharmacology review.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Table 5: Clinical Studies in Support of (b) (4) Lutrate (b) (4)

Phase	Study ID (Title)	Number of Patients	Key Objectives	Key Design Elements

(b) (4)				
	GP/C/05/PRO Efficacy and Safety of a New Leuprolide Acetate 22.5 mg Depot Formulation in the Treatment of Prostate Cancer	N=163	*"Proportion of successful patients achieving castration (testosterone ≤0.5 ng/mL) at Days 28, 84, and 168, and maintaining castration through Day 168"*	Open-label, single-arm study, with two doses of Lutrate 22.5 mg administered intramuscularly on Days 0 and 84
(b) (4)				

5.2 Review Strategy

Based on the study design and reported results (b) (4) the reviewers examined the study protocols, statistical analysis plans, submitted datasets and study reports. The key focus was on evaluating whether castration was achieved and maintained (b) (4) The reviewers conducted independent analyses (Section 6.1.3) based on the reported testosterone values from the central laboratory. These analyses addressed issues concerning patients with missing values and or testosterone surges, and generated results to reliably assess the clinical effectiveness of the two Lutrate formulations in terms of achieving and maintaining castration in each evaluable population. Analyses in the Per Protocol population were also performed to evaluate data consistency.

Safety evaluation focused on any signals that appeared specific to the (b) (4) products and examined key laboratory abnormalities well-known to occur with approved GnRH analogs. In addition, special attention was paid to adverse reactions or issues related to the Warnings common to approved GnRH analogs.

5.3 Discussion of Individual Studies

(b) (4)

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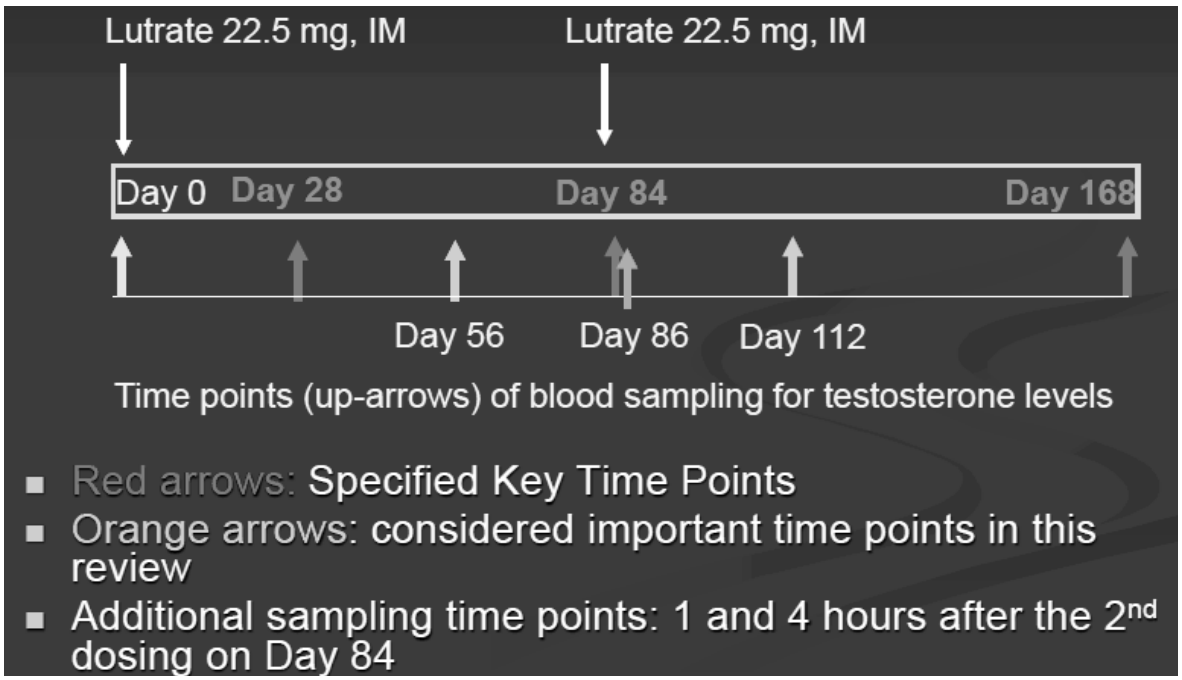
(b) (4)

Study GP/C/05/PRO

Design of Study GP/C/05/PRO

Study GP/C/05/PRO was an open-label, single-arm study of GP-Pharm's Lutrate (leuprolide acetate 22.5 mg) in patients with histologically proven carcinoma of the prostate who might benefit from medical androgen deprivation therapy. Its key objective was to investigate the efficacy and safety of the product administered for 2 doses with a 3-month interval. The primary endpoint was the proportion of patients who achieved castration at Days 28, 84, and 168, and maintained castration through Day 168. As shown in Figure 2, patients received Lutrate 22.5 mg intramuscularly on Day 0 and Day 84, and their testosterone levels were assessed at the protocol specified time points from Day 0 through Day168 (Table 9) . Safety assessment was performed throughout the study according to Study Calendar (Table 9).

Figure 2: Schematic Diagram of Study Design for GP/C/05/PRO



Protocol Amendments (GP/C/05/PRO)

No protocol amendments were introduced after the study initiation. Key protocol milestones of this study are listed in Table 8.

Table 8: Protocol Milestones of Study GP/C/05/PRO

Milestone	Date	Comments
Protocol	07-08/2011	The protocol planned to enroll 160 patients. See the sample size below.
Study Initiation	10/2011	First patient enrolled into the study
Pre-NDA Meeting	10/2012	The Agency recommended that a Kaplan-Meier analysis be conducted for this study to examine castration maintenance over time. In the K-M analysis, escape from a castrate testosterone level should be considered an event.
Enrollment Completion	12/2012	The last patient was enrolled.
Study Report	07/2014	
NDA Submission	07/31/2014	Submission of the datasets

Objectives (GP/C/05/PRO)

- "*To determine the proportion of successful patients achieving chemical castration (defined as castrate testosterone levels ≤0.5 ng/mL) at Days 28, 84, and 168, thereby demonstrating maintenance of castration through Day 168, with no missing data at these key time points*"

- To evaluate the safety of this new formulation of leuprolide acetate 22.5 mg

- To evaluate the pharmacokinetics (PK) and the pharmacodynamics (PD) of leuprolide acetate 22.5 mg

Key Eligibility Criteria (GP/C/05/PRO)

- Males ≥18 years of age
- Histologically proven carcinoma of the prostate
- Might benefit from medical androgen deprivation therapy
- Life expectancy at least 1 year
- ECOG Performance Status score of 0-2

- Adequate renal function at screening as defined by serum creatinine ≤1.6 times the ULN (upper limit of normal) for the clinical laboratory
- Adequate and stable hepatic function (<Grade 2 in ALT, AST, and total bilirubin)
- Testosterone level of ≥1.5 ng/mL at screening
- No history of orchiectomy, adrenalectomy, or hypophysectomy.
- No evidence of spinal cord compression, severe urinary tract obstruction, excruciating or severe pain from bone metastases, or brain metastases
- No prior androgen ablative therapy (including degarelix) within 12 months or lasting >6 months
- No use of androgen receptor inhibitors within 3 months
- No previous systemic cancer therapy such as chemotherapy, immunotherapy (e.g., antibody therapies, tumor vaccines), biological response modifiers (e.g., cytokines)
- No history of hypersensitivity to GnRH, GnRH agonists, including any LHRH analogues, or any excipients of the study formulation
- No uncontrolled diabetes
- No uncontrolled congestive heart failure, myocardial infarction or a coronary vascular procedure (e.g. balloon angioplasty, coronary artery bypass graft) or significant symptomatic cardiovascular disease(s) within 6 months before baseline;
- No uncontrolled hypertension or symptomatic hypotension within 3 months
- Signed informed consent before any study related activity

Reviewer's Comments: (b) (4) *The key difference is that patients who received prior ADT were allowed if the prior therapy did not last for >6 months and was >12 months before screening. This is acceptable provided that their baseline testosterone level was not less than 1.5 ng/mL.*

Study Treatment (GP/C/05/PRO)

Patients received Lutrate 22.5 mg depot intramuscularly on Days 0 and 84. The study medicine was provided as Clinical Batch 10311-1.

Prohibited medications and or treatments (b) (4) Use of degarelix and other systemic therapies were not allowed in this study.

Study treatment could be discontinued for patient withdrawal or at the discretion of the investigator for adverse reaction, concurrent illness, or failure to comply with the protocol.

Efficacy Assessments and Safety Monitoring (GP/C/05/PRO)

To assess whether patients achieved (at Day 28) and maintained castration through the end of study (Day 168), blood samples for testosterone levels were collected at the protocol-specified time points (Table 9) and were assayed in the central laboratory. Results from this laboratory were used for the planned primary endpoint analysis. Similarly, samples LH, FSH, and PSA were also collected and sent to the same laboratory for their level determination.

Adverse events/reactions and changes in ECG and laboratory parameters were monitored and assessed according to the Study Calendar (Table 9). The severity of adverse events was graded and captured using the Common Terminology Criteria for Adverse Events (CTCAE v. 3).

Table 9: Study Calendar for GP/C/05/PRO

Visits (V)	V1 Screening	V2 Baseline	V3	V4	V5	V6	V7	V8	V9	V10[a]	Follow-up phone call
Days (D)	*-14/-1*	*D0 ±2[i]*	*D2 ±2[i]*	*D14 ±2[i]*	*D28 ±2[i]*	*D56 ±2[i]*	*D84 ±2[i]*	*D86 ±2[i]*	*D112 ±2[i]*	*D168 ±2[i]*	*1-2 weeks after final visit(V10)*
Informed consent	X										
Inclusion/exclusion	X	X									
Demography, lifestyle, height	X										
Fasting[b]	X	X			X		X		X	X	
Medical history	X										
Physical examination and weight	X	X			X		X		X	X	
Vital sign measurements (including temperature)	X	X			X	X	X		X	X	
Electrocardiogram	X	X[c]			X		X		X	X	
Clinical safety laboratory tests	X[d]				X		X		X	X	
Bone pain, urinary pain, and urinary symptoms		X	X	X	X	X	X	X	X	X	
Assessment of hot flushes		X	X	X	X	X	X	X	X	X	
WHO/ECOG performance status	X	X		X	X	X	X		X	X	
Study drug administration		**X**					**X**				
Testosterone level[e]	X[f]	X	X	X	X	X	X	X	X	X	
LH and FSH level[e]		X	X	X	X	X	X	X	X	X	
PSA[g]		X		X	X	X	X		X	X	
Pharmacokinetic blood sample[h]		X	X	X	X	X	X	X	X	X	
Local tolerability assessments		X					X				
Previous/concomitant treatments	X	X	X	X	X	X	X	X	X	X	X
Adverse event monitoring		X	X	X	X	X	X	X	X	X	X
Dispense diary to patient		X			X	X	X		X		
Review diary from patient			X	X	X	X	X	X	X	X	

ECOG = Eastern Cooperative Oncologic Group; FSH = follicle-stimulating hormone; LH = luteinizing hormone; PSA = prostate-specific antigen; WHO = World Health Organization

[a] All Visit 10 (Day 168) procedures will be performed for any patient who withdraws prematurely from the study whenever possible.

[b] Patients must be fasting (no food or drink within 8 hours before the study visit).

[c] Electrocardiogram is performed at the baseline visit only if the screening electrocardiogram was done ≥8 days before.

[d] Clinical safety laboratory samples are collected at the screening visit, and visits 5, 7, and 9, and 10.Clinical safety laboratory assessments include coagulation (prothrombin time/partial thromboplastin time at Screening only), hematology, chemistry, and urinalysis. Patients must be enrolled within 14 days of the screening visit.

[e] On Days 0 and 84, blood samplings for testosterone, LH, and FSH will be collected before dosing and 1 and 4 hours after dosing.

[f] Testosterone level at Screening will be determined at the clinical center as part of the clinical safety laboratory analysis (for inclusion, screening testosterone level must be ≥1.5 ng/mL).

[g] Each PSA sample will be divided into 3 aliquots; analysis of one PSA aliquot will be performed by the local laboratory of each clinical site; two PSA aliquots will be stored at a central site and analyzed at the end of the trial (if not before) by Nuvisan, Germany.

Statistical Methods (GP/C/05/PRO)

Analysis Populations (per the applicant's SAP)

- The "ITT" population: to include patients who received at least 1 dose of study treatment and had at least 1 efficacy assessment after the first dose.
- The evaluable population was defined as the total number of patients with data at one or more of the key time points (i.e., Day 28, 84 and 168).
- The per-protocol (PP) population: to only include patients who completed all visits per protocol and received all doses of study drug.
- The safety population: to include all enrolled patients who received at least 1 dose of the study drug

Sample Size

The null hypothesis was that the percentage of successful patients in the population was less than the reference proportion, i.e., H_0: p = 93% versus H_A: p = 98%. A 2-sided exact test for the single proportion at a 5% significance level would have 80% power to detect a difference between the null hypothesis 93% and the alternative 98% when the sample size was N = 144. . With a maximum dropout rate of 10%, the study planned to enroll 160 patients.

Primary Endpoint Analysis

The primary analysis was to assess the percentage of successfully treated patients in the evaluable population with testosterone ≤ 0.5 ng/mL (i.e., $N_{\text{successes}}/N_{\text{evaluable patients}}$) at Days 28, 84, and 168. The goal was to demonstrate the achievement and maintenance of castration through Day 168 with no missing data at the key time points.

For each patient, if testosterone was greater than 0.5 ng/mL or if testosterone data were missing at any of the key time points (i.e., Days 28, 84, and 168), the patient would be classified as a failure, unless the missing data were due to an event unrelated to study drug such as death.

Testosterone levels at other time points (i.e., Day 56, Day 86, Day 112, and 1 and 4 hours after the second dose on Day 84) were planned to further characterize individual patient data. Missing data at such time points would be handed with the LOCF method.

Based on testosterone concentrations throughout the study, an exact 2-sided binomial test was planned to examine the study "success" at the reference (null hypothesis) castration rate of 93% versus the alternative rate of 98%.

Reviewers' comments:

The statistical plan for evaluating the primary endpoint was based on an exact 2-sided binomial test of a point estimate of the percentage of patients who achieved and maintained castrate testosterone levels on Days 28, 84, and 168. Results of the test could be affected by the amount of missing data at the three key time points, since patients would be considered "successful" in achieving or maintaining castration if the missing data was assessed as unrelated to study drug. This may introduce bias in an open-label study since it was necessary to determine whether a missing data point was related or unrelated to study drug. The statistical plan did not discuss issues related to testosterone levels at the other time points. To better address issues concerning missing data and testosterone surges in the study, it is more suitable to use the Kaplan-Meier method for analysis of the maintenance of castration.

6 Review of Efficacy

6.1 Indication

The proposed indication [redacted] (b) (4) is for the palliative treatment of patients with advanced prostate cancer.

6.1.1 Methods

The clinical and statistical reviewers evaluated [redacted] (b) (4) studies according to the strategies listed in Section 5.2. The reviewers examined the submitted datasets and verified the completeness of the datasets and data consistency with the findings described in the study reports. The reviewers also assessed the applicant's reported analyses and conducted independent analyses. Issues identified during the review were discussed in order to reliably determine the castration efficacy [redacted] (b) (4).

6.1.2 Demographics

[redacted] (b) (4)

For Study GP/C/05/PRO (Lutrate Depot 22.5 mg), 163 patients were enrolled from 25 study sites in the USA. Their demographic and baseline disease characteristics are shown in Tables 10 and 11, respectively.

Table 10: Demographics of Patients in [redacted] GP/C/05/PRO

	[redacted]	**GP/C/05/PRO** (N=163)
Age Median (Range)		72 (47, 91)
Race (%)		
Caucasian		101 (62%)
African American		49 (30%)
Other		13 (8%)

Table 11: Disease Characteristics in [redacted] GP/C/05/PRO

	[redacted]	**GP/C/05/PRO** (N=163)
Disease Stage (%)		
Metastatic		18 (11%)
Non-Metastatic		145 (89%)
Unknown		0
Testosterone (ng/mL) Median (Range)		3.85* (0.63, 9.9)
PSA (ng/mL) Median (Range)		6.5 (0.4, 935)
**Based on Day 0 pre-dose testosterone levels*		

Reviewer Comments:
Both studies only had a small percentage (5-11%) of patients with metastatic prostate cancer in whom use of a GnRH analog is generally indicated. It is not clear how many patients without metastatic disease would benefit from use of a study product that was intended to achieve androgen deprivation.

Patient Treatment and Disposition

All patients enrolled [redacted] received their first treatment on Day 0. [redacted] one in Study GP/C/05/PRO withdrew

from their study before Day 28, making them not evaluable for determination of castrate levels of testosterone by Day 28. The rest of patients had study treatment between Day 28 and Day 168. Table 12 lists patient disposition [redacted] Note that [redacted] there were no deaths during Study GP/C/05/PRO.

Table 12: Patient Disposition in [redacted] GP/C/05/PRO

	[redacted]	**GP/C/05/PRO** (N=163)
Completed Study (%)		151 (93%)
Withdrawn and or Discontinued (%) Before Day 28 After Day 28		 1 (<1%) 11 (7%)
**Including 2 patients who discontinued due to adverse events: Patient [redacted] was hospitalized for his knee surgery and Patient [redacted] had an abdominal aortic aneurysm.* *There was no discontinuation due to adverse events in Study GP/C/05/PRO.*		

Key protocol violations and deviations are summarized in Table 13. Patients who did not complete all protocol visits and/or receive all scheduled doses (without major violations) were not included in the per-protocol (PP) populations according to the protocol definition as listed in Section 5 of this review. None of the listed violations and or deviations were considered to significantly affect the evaluation of the achievement and maintenance of castration in the evaluable population.

Table 13: Key Protocol Violations and Deviations

	[redacted]	**GP/C/05/PRO** (N=163)
Criteria Unmet		2
Use of Prohibited Treatments**		7
Patients who did not complete all protocol visits and or receive all scheduled doses***		29
Note: Some patients had more than one violation and or deviations. [redacted]		

ng/mL. This patient was not included in the evaluable population as he was discontinued from the study before Day 28.

***Prohibited treatments included use of androgen receptor inhibitors (e.g.,bicalutamide) and radiation therapy. One patient [redacted] in Study GP-C-05-PRO received a dose of Trelstar one week before his last visit on Day 168. He had castrate levels of testosterone during the study.*

****Based on the statistical assessment of relevant datasets in the submission.*

With the above information, three populations as shown in Table 14 were identified for efficacy and safety analyses. For each evaluable population, this review included one additional patient as listed in the footnote of this table. The applicant excluded the two patients from their evaluable population for incomplete dosing or the investigator's unresponsiveness to inquiries. Given the study design and central laboratory determination of blood testosterone levels, the two patients should be included and considered evaluable for determination of castration.

Table 14: Populations for Efficacy and Safety Analyses

[redacted]	**GP/C/05/PRO** (N=163)
Evaluable Population*	**162**
PP**	134
Safety Population	**163**

**Excluding patients who dropped out before Day 28 in Table 12. Patient [redacted] was included for the [redacted] study since he had testosterone values from Day 28 through Day 168. Similarly, Patient [redacted] in the 22.5 mg study was included as he had testosterone values available from the central laboratory despite the use of radiotherapy during the study.*

***Excluding patients who did not complete all protocol visits and or receive all scheduled doses of study treatment*

Review Comments:
The evaluable population of [redacted] GP-Pharm's Lutrate depot will be the basis for the primary analysis and interpretation of the effectiveness of [redacted] depot. Analysis results from the PP population will be used to help examine data consistency.

6.1.3 Analysis of Primary Endpoint(s)

[redacted]

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Analysis of Primary Endpoint in Study GP/C/05/PRO (for the 22.5 mg formulation)

The primary endpoint for this study was "Proportion of successful patients achieving castration (testosterone ≤0.5 ng/mL) at Days 28, 84, and 168, and maintaining castration through Day 168".

The proportion of patients who achieved castrate levels of testosterone by Day 28 was assessed and the results are shown in Table 21. In the evaluable population, 96.9% of patients achieved castration by Day 28. This castration rate is similar to the applicant's reported castration rate of 98.7%, indicating that Lutrate 22.5 mg was efficacious in achieving castration in >90% of study patients at Day 28. Note that the applicant did not include 2 patients with missing data on Day 28 in the calculation.

Table 21: Proportion of Patients Who Achieved Castration on Day 28 in Study GP/C/05/PRO

	Evaluable (N=162)	**PP (N=134)**
Number of Patients with a testosterone level of ≤0.5 ng/mL on Day 28	157	132
Castration Rate (95% CI)	96.9*% (92.9%; 99.0%)	98.5% (94.7%; 99.8%)
**Two patients (b) (6) who had missing data on Day 28 were treated as "failure" in this review since their testosterone levels immediately prior to the missing data were >0.5 ng/mL.*		

To evaluate the proportion of patients who maintained castration from Day 28 through Day 168, the Kaplan-Meier method was used to calculate the cumulative probability of maintenance of castration. The reason is that the reviewers found numerous testosterone surges and missing data throughout the study. Table 22 lists patients with testosterone surges without missing data and Table 23 summarizes those with missing data and or testosterone surges. It would be difficult to address these issues in a binomial test.

Table 22: Patients with Testosterone Surges without Missing Data in Study GP/C/05/PRO

	Patient ID	**Time of Testosterone Surges** (>0.5 ng/mL)
1	(b) (6)	Day 84 4H postdose
2		Day 168

3	(b) (6)	Days 56, 84 1H postdose, 84 4H postdose
4		Day 86
5		Day 56
6		Days 28, 56
7		Day 112
8		Day 112
9		Days 84 pre-dose, 168
10		Day 86
11		Day 56
12		Day 112
13		Day 84 4H postdose
14		Day 86
15		Days 28, 112
16		Day 56
17		Day 86
18		Day 84 1H postdose
19		Day 84 1H postdose
20		Day 56
21		Day 84 1H postdose
Patients with a testosterone surge at any of the key time points were highlighted in yellow.		

Table 23: Patients with Missing Data in Study GP/C/05/PRO

	Patient ID	**Missing Data** (Time Points)	**Testosterone Surges** (>0.5 ng/mL)	**Failure (Event)/ No Surges (Non-event) with Time from Day 28 Used in the FDA Analysis**
1	(b) (6)	Day 86	—	No surges from Day 28 through Day 168
2		Day 84 4H postdose	—	No surges from Day 28 through Day 168
3		Days 56, 84 predose, 84 1H postdose, 84 4H postdose, 86, 112	—	No surges from Day 28 through Day 168
4		Day 84 predose	—	No surges from Day 28 through Day 168
5		Day 112	—	No surges from Day 28 through Day 168
6		Day 112	—	No surges from Day 28 through Day 168
7		Days 84 1H postdose, 84 4H postdose	Day 168	Failure, on Day 168
8		Days 84 1H postdose, 84 4H postdose, 112, 168	—	No surges from Day 28 through Day 86; Censored Day 86
9		Day 84 1H postdose	Day 56	Failure, on Day 56
10		Day 84 4H postdose	—	No surges from Day 28 through Day 168
11		Day 56	—	No surges from Day 28 through Day 168
12		Days 84 predose, 84 1H postdose, 84 4H postdose, 86, 112	Day 28	Failure, on Day 28
13		Day 28	—	Uncertain: considered no surges from Day 28 through Day 168

14	[redacted] (b) (6)	Day 112	Days 86, 168	Failure, on Day 86
15		Days 56, 84 predose, 84 1H postdose, 84 4H postdose, 86, 112	—	No surges from Day 28 through Day 168
16		Day 112	—	No surges from Day 28 through Day 168
17		Days 84 predose, 84 1H postdose, 84 4H postdose, 86, 112	—	No surges from Day 28 through Day 168
18		Days 28, 84 1H postdose, 84 4H postdose	—	Uncertain: considered no surges from Day 28 through Day 168
19		Day 112	—	No surges from Day 28 through Day 168
20		Day 84 1H postdose	—	No surges from Day 28 through Day 168
21		Days 84 1H postdose, 84 4H postdose	Day 56	Failure, on Day 56
22		Day 84 4H postdose	—	No surges from Day 28 through Day 168

Including patients with missing data who also had testosterone surge(s). Patients with a testosterone surge at any of the key time points were highlighted in yellow.

Two patients [redacted] (b) (6) *highlighted in gray, were considered to have "uncertain" status on Day 28 since they had a non-castrate level of testosterone on Day 14 with missing data on Day 28. Data was missing due to either a missed visit or inadequate samples. The rest of testosterone levels after Day 28 show that they maintained castration during the study. As such, they were classified as "No surges from Day 28 through Day 168" in the analysis of castration maintenance (Table 24).*

Based on the information contained in Tables 22 and 23, a Kaplan-Meier analysis was performed. As shown in Table 24, the cumulative probability of castration maintenance was 83.9% (95% CI: 77.3%, 88.8%) in the evaluable population, indicating that Lutrate 22.5 mg was not efficacious in maintaining castration. Similar results were found in the PP population.

Table 24: Proportion of Patients Maintaining Castration in Study GP/C/05/PRO

	Evaluable (N=162)	**PP (N=134)**
Number of patients maintaining a testosterone level of ≤0.5 ng/mL from Day 28 through Day 168	136	115
Castration Rate (95% CI)	83.9*% (77.3%, 88.8%)	85.8% (78.7%, 90.7%)

The castration maintenance rate would be 82.7% (95% CI: 75.9%, 87.7%) if the two patients categorized as "Uncertain" (Table 23) were considered "failure" in the Kaplan-Meier analysis. When these two patients were excluded from the analysis due to the missing data, the castration maintenance rate was 83.7% (95% CI: 77.0%, 88.6 %).

Our review findings are different from the results of the Applicant's analysis (Table 25). This analysis ignored some detected testosterone surges (including a few surges at the end of study), leading to an overestimation of the rate of castration maintenance.

Table 25: Applicant's Reported Proportion of Patients Who Reached Castration in Study GP/C/05/PRO

	Total (N=161) n (%)
Number of Evaluable Patients	161
Number of Successful Patients	158 (98.1)
Number of Failed Patients	3 (1.9)
Two-Sided Exact 95% Confidence Interval of the Percentage of Successful Patients	94.7-99.6

Adapted from Applicant's CSR Page 70. Note that one patient [redacted] was not included in the applicant's evaluable population.

Reviewer's Comments:

The above results show that GP-Pharm's Lutrate [redacted] 22.5 mg were able to achieve castration on Day 28 but were not efficacious in maintaining castration from Day 28 through Day 168. Most of the testosterone surges occurred within one week after the second dose (Tables 17 and 23), suggesting [redacted] formulation might not sufficiently or completely desensitize the pituitary in some patients, making the gland still sensitive to the agonistic stimulation of leuprolide acetate. This may be related to the quality [redacted] that might not consistently deliver the intended leuprolide dose as intended or maintain a sufficient leuprolide level in the circulation at the end of the first dose. Such possibilities may be supported by the [redacted]% product overfill per vial as identified in the CMC review. Given the inadequate castration maintenance and the CMC issues, the reviewers recommend that Applicant conduct new studies [redacted] with batches acceptable from a CMC perspective.

6.1.4 Analysis of Secondary Endpoints(s)

Evaluation of the secondary endpoints [redacted] does not provide substantial evidence for the intended indication, since [redacted] was not

efficacious in maintaining castration during the study (Section 6.1.3). In addition, key secondary endpoints (e.g., changes in PSA or LH) were part of the pharmacological actions known to androgen deprivation therapy and were considered supportive when the primary endpoint of maintaining castration was met.

6.1.5 Subpopulations

Given the findings described in Section 6.1.3 and the small sample size of (b) (4) study, subpopulation analyses are not clinically relevant.

6.1.6 Analysis of Clinical Information Relevant to Dosing Recommendations

For (b) (4) Lutrate, there was only one dosing schedule used in the (b) (4) study.

6.1.7 Discussion of Persistence of Efficacy and/or Tolerance Effects

(b) (4) studies were conducted with a total of 6 months of monitoring blood testosterone levels at various time points. Persistence of effectiveness beyond 6 months remains unknown.

No evidence has shown that GnRH analogs induce tolerance with continued dosing.

6.1.8 Additional Efficacy Issues/Analyses

None

7 Review of Safety

7.1 Methods

The reviewer evaluated the safety profile of (b) (4) Lutrate (b) (4) based on the submitted adverse event datasets and laboratory results. For patients who had SAEs, data consistency and outcomes were examined across relevant datasets along with the information provided in CRFs and narratives. Special attention was paid to adverse reactions known to GnRH analogs or androgen deprivation.

Treatment-emergent adverse events (TEAEs) included any new adverse events reported during the study, and treatment-related adverse events (TRAEs) were tabulated according to the Investigator's reported attribution assessments.

7.1.1 Clinical Studies Used to Evaluate Safety

The safety evaluation (b) (4) GP-Pharm Lutrate (b) (4) was based on the data (b) (4) listed in Section 5.1.

7.1.2 Adequacy of Data

The reviewers considered the submitted data adequate for the safety evaluation based on the submitted safety datasets, mainly including information on exposure, adverse events, concomitant medications, physical examination, vital signs and laboratory results.

(b) (4)

[redacted]

7.2 Adequacy of Safety Assessments

Based on the safety assessment schedules (Section 5.3) and submitted safety datasets, short-term toxicities of the Lutrate formulations appear to be adequately evaluated. [redacted] that the safety profile of leuprolide has been known for over two decades, safety information [redacted] is sufficient to characterize the adverse reactions [redacted] Nevertheless, the long-term (e.g, over years) safety [redacted] could not be assessed due to the study period of 6 months (Section 7.2.1).

7.2.1 Overall Exposure at Appropriate Doses/Durations

[redacted]

In Study GP/C/05/PRO, 157 of the total 163 patients received 2 protocol-required doses of Lutrate 22.5 mg and 151 patients completed the study. The duration of exposure was about 6 months as well.

7.2.2 Explorations for Dose Response

Not applicable

7.2.3 Special Animal and/or In Vitro Testing

Not applicable

7.2.4 Routine Clinical Testing

All study patients were monitored with periodic physical and routine laboratory examinations according to the study calendars discussed in Section 5.3. Adverse events were assessed at every scheduled visit. This was adequate to determine the adverse event profiles of the products.

7.2.5 Metabolic, Clearance, and Interaction Workup

There was no drug-drug interaction study conducted for this NDA. See clinical pharmacology review for additional PK information.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Common adverse events from use of leuprolide or other GnRH analogs in men are related to castrate levels of testosterone. These generally include hot flushes, fatigue, headache, GI disturbances, erectile dysfunction, decreases in bone density or osteoporosis, increases in the risk of developing diabetes and fatal cardiovascular disease. Their incidences may be associated with the duration of exposure. Metabolic changes such as diabetes and the increased risk of cardiovascular disease may occur after long-term use.

7.3 Major Safety Results

7.3.1 Deaths and Serious Adverse Events

Deaths:

(b) (4)

There were no deaths in Study GP/C/05/PRO.

SAEs:

(b) (4)

(b) (4)

In Study GP/C/05/PRO, 14 SAEs (Table 28) were reported in 12 patients. Three of them were syncope, which was transient and resolved without complications. One SAE was myocardial infarction which occurred 135 days after the start of study treatment. The patient was hospitalized for 2 days during which the SAE resolved.

Another important SAE was diabetic ketoacidosis, which occurred 114 days after the study treatment initiation in a patient who were taking lisinopril and simvastatin. At diagnosis, his fasting glucose was 632 mg/dL, much higher than the previous fasting glucose levels he had (123,146, 209 mg/dL at Baseline, Days 28 and 84, respectively). The patient was hospitalized for 5 days and discharged with metformin and glyburide. At the Day 168 visit, his fasting glucose level was 178 mg/dL. The investigator's causality assessment was that this event was unrelated to study treatment.

Table 28: Reported SAEs in Study GP/C/05/PRO

	Safety Population (N=163)
Number of SAEs (%)	14 (9%)

SAE*	Diarrhea Myocardial infarction Syncope Cardiac failure congestive Pneumonia Syncope Inguinal hernia, obstructive Benign neoplasm of bladder Diabetic ketoacidosis Fall Syncope Dehydration Non-cardiac chest pain Rectal hemorrhage
Two patients had an additional SAE each. **All the listed SAEs were reported to be unrelated or unlikely related to study treatment.*	

Reviewer's Comments: *The above SAEs include hyperglycemia, worsening Type-2 diabetes, and diabetic ketoacidosis. In the reviewer's assessment, the diabetic SAEs might be attributed to a worsening of glycemic control by ADT. This may be exemplified by the gradual increase in Fasting Glucose Levels with study duration in the case of the patient with diabetic ketoacidosis. On the other hand, the Investigator's assessment of the same SAEs considered the causality as "unrelated or unlikely related" to study treatment. This difference may reflect challenges or uncertainty in the causality assessment in single-arm, open-label studies.*

7.3.2 Dropouts and/or Discontinuations

[redacted] (b) (4) No patients discontinued due to an adverse event in Study GP/C/05/PRO.

7.3.3 Significant Adverse Events

Based on the Investigator's reported causality assessments, key adverse events that were considered possibly, probably or certainly related to study treatment were hot flushes, fatigue, injection site pain and hyperhidrosis (Table 29). These events are generally consistent with the results from the pooled analysis (Table 26) and the individual study analysis (Tables 30 and 31). Except for injection site pain, the other adverse events represent common reactions known to occur with ADT.

There were no hypersensitivity and allergic reactions reported in the two studies.

Table 29: Important Treatment-Related Adverse Events Reported in [redacted] GP/C/05/PRO

	[redacted]	Study GP/C/05/PRO (N=163)
Hot Flushes		126 (77%)
Fatigue		16 (10%)
Injection Site Pain		15 (9%)
Hyperhidrosis		5 (3%)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Commonly reported treatment-emergent adverse events or reactions [redacted] with an incidence of ≥ 10% were tabulated regardless of their causality. The results are shown in [redacted] Table 31 (for the 22.5 mg study). Adverse events [redacted] were hot flushes, arthralgia, fatigue, injection site pain, headache, and diarrhea. The majority of them were mild or moderate in the severity. Of them, hot flushes, fatigue, and injection site pain were attributed to study treatment (Table 29).

[redacted]

(b) (4)

Table 31: Common Adverse Events Reported in Study GP/C/05/PRO

	Safety Population (N=163)	
	All Grade	**Grade 3-4**
Hot Flushes	127 (%)	5 (%)
Diarrhea*	21 (%)	2 (%)
Pollakiuria	20	0
Arthralgia	18 (%)	0 (%)
Injection Site Pain	18 (%)	0 (0%)
Fatigue	17 (%)	0 (0%)
**Nineteen events were assessed as unrelated to study treatment.*		

7.4.2 Laboratory Findings

Safety laboratory parameters were monitored (b) (4) and the results were categorized as low, normal, or high. Patients in each category were listed according to visit times in the NDA submission, and the Applicant reported that overall none of the changes were considered clinically relevant by the Investigators.

The reviewer evaluated important laboratory parameters known to be affected by GnRH analogs, including CBC, hepatic transaminases, glucose and creatinine. To assess the severity, reported values of the parameters during the study were graded according to the current NCI CTCAE v4 criteria. The findings are shown in Table (b) (4) 33.

Among the abnormalities, hyperglycemia appeared to be the most common in the two studies and a few patients had a Grade 3-4 elevation, including one patient who had diabetic ketoacidosis diagnosed (Section 7.3.1) 3 months after study treatment. This highlights the importance of monitoring glucose in patients treated with a GnRH analog. In addition, elevations in hepatic transaminases and creatinine were also detected. (b) (4)

(b) (4)

Table 33: Important Laboratory Abnormalities in Study GP/C/05/PRO

	Safety Population (N=163)	
	All Grade	**Grade 3-4**
Hyperglycemia*	127 (78%)	9 (6%)
Decrease in Hemoglobin	95 (58%)	0 (0%)
Increase in ALT/AST	35 (21%)	0 (0%)
Increase in Creatinine	6 (4%)	0 (0%)

Monitored on Days 28, 84, 112, and 168

**At screening, 92 patients (56%) had hyperglycemia and of them, 3 patients had Grade 3 hyperglycemia.*

7.4.3 Vital Signs

Vital signs including body temperature were monitored according to the study calendars (Tables 7 and 9). No significant trends or changes were observed.

7.4.4 Electrocardiograms (ECGs)

ECGs were monitored in the two studies according to the Study Calendars (Tables 7 and 9). There were no ECG waveforms submitted to the ECG warehouse for evaluation [redacted] (b) (4) Based on the Applicant's submitted ECG datasets, the reviewer examined whether there were patients with a severe prolongation of the QT interval.

[redacted] (b) (4)

In Study GP-C-05-PRO, three patients [redacted] (b) (6) with a QT interval of >500 ms at baseline were enrolled and their QT intervals remained

of >500 ms during the study. None of them had a symptomatic arrhythmia or cardiac adverse event reported. There were no patients who had a QT interval of >500 ms newly detected in two separate ECGs while on study.

Reviewer's Comments:
There was no criterion for QT interval in the eligibility requirements for the two studies. The QT interval prolongation could not be fully evaluated in the absence of ECG waveforms. Some of the above cases appear consistent with the current QT/QTc warning in the label of approved GnRH analogs.

7.4.5 Special Safety Studies

None

7.4.6 Immunogenicity

Not assessed in the study.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable since the study patients received the scheduled doses in each study.

7.5.2 Time Dependency for Adverse Events

A 6-month study interval was available for adverse event assessment in both studies. This interval was insufficient to adequately assess the occurrence of adverse events over time.

7.5.3 Drug-Demographic Interactions

Drug-demographic interactions for safety are not explored since the effectiveness (b) (4) could not be reliably established with the current clinical data (Section 6.1.3) and CMC deficiencies (Section 4.1).

7.5.4 Drug-Disease Interactions

Unable to assess in these short-term, single-arm studies

7.5.5 Drug-Drug Interactions

Not studied in this NDA.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Potential carcinogenicity has not been suggested with GnRH analogs.

7.6.2 Human Reproduction and Pregnancy Data

There were no reports of pregnancy in the female partners of men enrolled in (b) (4)

7.6.3 Pediatrics and Effect on Growth

Not applicable for this NDA.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdose was reported. The product has no known abuse potential in men.

8 Postmarketing Experience

Not applicable.

9 Appendices

9.1 Literature Review/References

Inserted as footnotes

9.2 Labeling Recommendations

Labeling was not initiated because of deficiencies identified during the review.

9.3 Advisory Committee Meeting

This application was not referred to the Oncologic Drugs Advisory Committee since this NDA has numerous deficiencies identified during the review.

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/s/

YANGMIN NING
04/24/2015

HUI ZHANG
04/24/2015

SHENGHUI TANG
04/24/2015

VIRGINIA E MAHER
04/24/2015

Clinical Pharmacology Review	
NDA	**205054**
Submission Date:	**July 31, 2014**
Applicant:	**GP-Pharm S.A**
Generic Name:	**LUTRATE DEPOT (Leuprolide Acetate for Depot Suspension)**
Formulation/Strength:	**(b) (4) 22.5 mg Injection in a Kit with a Vial, a Prefilled Syringe and a Transfer Device**
OCP Reviewer:	**Pengfei Song, Ph.D.**
OCP Team Leader:	**Elimika Pfuma, Ph.D.**
OCP Division:	**Division of Clinical Pharmacology V (DCPV)**
ORM Division:	**Division of Oncology Products 1 (DOP1)**
Submission Type; Code:	**Original-1 (Type 5- New Formulation or New Manufacturer)**
Indication:	**Palliative Treatment of Advanced Prostate Cancer**
Dosing Regimen:	**(b) (4)** • **22.5 mg for 3 Months Administration, Given as a Single Intramuscular Injection Every 12 Weeks**

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1 EXECUTIVE SUMMARY

In this 505 (b) (2) new drug application (NDA), the applicant seeks approval of LUTRATE DEPOT (leuprolide acetate for depot suspension) (b) (4) 22.5 mg for three months for palliative treatment of advanced prostate cancer, with Lupron® Depot (b) (4) 22.5 mg, (b) (4) as the listed drug.

The applicant submitted the results of (b) (4) open-label, single-arm Phase 3 trials (b) (4) Study GP/C/05/PRO for 22.5 mg in 163 patients). The primary efficacy endpoint was the achievement and maintenance of castration (plasma testosterone level ≤ 0.5 ng/mL). Clinical and statistical reviews concluded that (b) (4) failed to meet the primary efficacy endpoint in the trials, and a complete response letter will be issued.

Pharmacokinetic (PK) data available from (b) (4) 30 patients in Study GP/C/05/PRO indicated that maximum plasma concentration (C_{max}) of leuprolide was achieved in approximately 2 hour after intramuscular injection. No obvious accumulation in plasma leuprolide concentrations was observed after repeated doses of (b) (4) LUTRATE DEPOT.

The Office of Scientific Investigation (OSI) inspection concluded that the bioanalytical assays used for the measurement of testosterone concentrations are acceptable.

1.1 RECOMMENDATIONS

This NDA application is acceptable from a clinical pharmacology perspective. However, as a complete response letter will be issued for this NDA, no labeling language agreement or post-marketing requirement/commitment is needed.

Signatures:

Pengfei Song, Ph.D.	**Elimika Pfuma, Ph.D.**
Reviewer	**Acting Team Leader**
Division of Clinical Pharmacology V	**Division of Clinical Pharmacology V**

Cc: DDOP: CSO - Charlene Wheeler; MTL - Viginia Maher; MO - Yangmin Ning;
DCP-5: DDD - Brian Booth; DD - Nam Atiqur Rahman

2 QUESTION BASED REVIEW

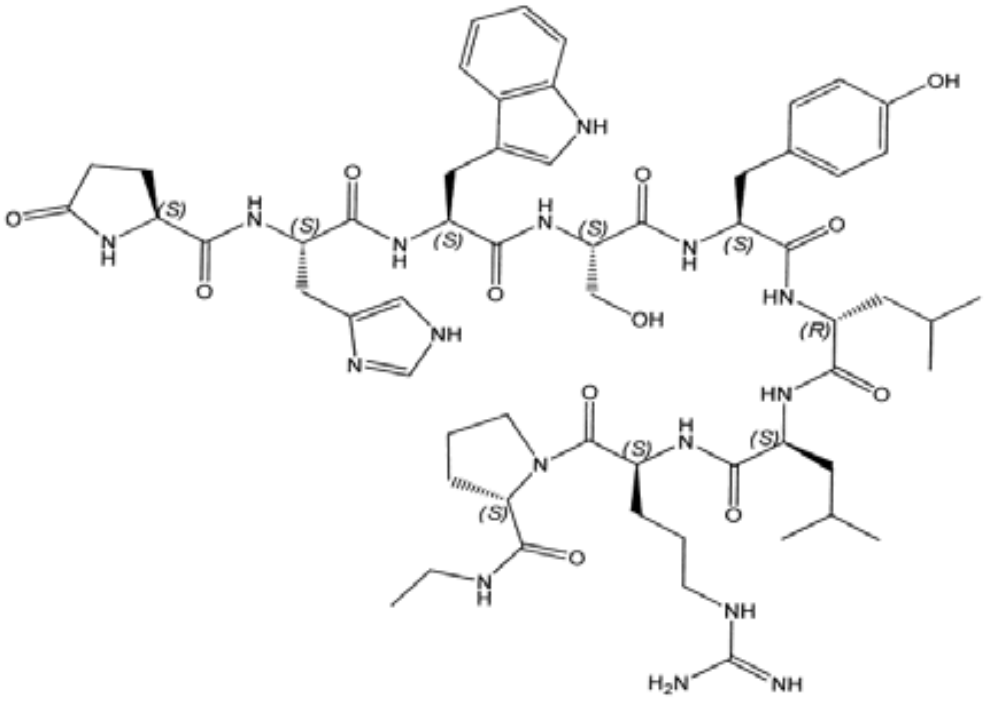
2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Leuprolide acetate is a synthetic nonapeptide analogue of leuteinizing hormone-releasing hormone (LHRH), also known as a gonadotropin releasing hormone (GnRH) analogue. Leuprolide acetate is a white to off-white powder with a molecular weight of 1209.4 (free base).

Physico-chemical properties of drug substance

1. Structural formula:



2. Established name: Leuprolide acetate
3. Molecular weight (free base): 1209.4
4. Molecular formula: $C_{59}H_{84}N_{16}O_{12}$
5. Chemical name (CAS): 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt)
6. Solubility: Soluble in water and methanol

2.1.2 What are the proposed mechanism of action and therapeutic indication?

LUTRATE DEPOT (leuprolide acetate for depot suspension) is a GnRH agonist proposed for the palliative treatment of advanced prostate cancer.

Leuprolide acetate is a potent agonist analogue of gonadotropin-releasing hormone (GnRH). Continuous administration of leuprolide in males decreases luteinizing hormone (LH), follicle-stimulating hormone (FSH), dihydrotestosterone (DHT), and testosterone concentrations by desensitizing and/or down-regulating the pituitary.

2.1.3 What are the proposed dosage and route of administration?

LUTRATE DEPOT is provided in a kit with a vial, a prefilled syringe and a transfer device: (b) (4)

- LUTRATE DEPOT 22.5 mg for 3 months administration, given as a single intramuscular injection every 12 weeks.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

In the current 505 (b) (2) NDA submission, the applicant seeks approval of LUTRATE DEPOT (Leuprolide acetate for depot suspension) (b) (4) 22.5 mg three-month strength for the palliative treatment of advanced prostate cancer, with Lupron® (b) (4) 22.5 mg under (NDA 020517) (Abbott), (b) (4) as the listed drug.

The applicant submitted the results of (b) (4) Study GP/C/05/PRO for the 22.5 mg strength in 163 patients). The primary efficacy endpoint was the achievement and maintenance of castration (plasma testosterone level ≤ 0.5 ng/mL) during the study course. Based on the clinical and statistical reviews, (b) (4) able to achieve medical castration on Day 28 but failed to maintain medical castration during the study course. Therefore, (b) (4) failed to meet the primary efficacy endpoint, and a complete response letter will be issued to this NDA submission based on this clinical issue (please see the clinical review by Dr. Yangmin Ning for more information), along with compliance and CMC issues.

The applicant submitted PK data obtained (b) (4)

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Table 1. LUTRATE DEPOT Clinical Trials with PK Data

Study Number Location Study Design	Objective(s) of the Study	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
(b) (4)					
GP/C/05/PRO Section 5.3.5.2 Open-label	Efficacy and safety; PK analysis in a sub group of patients (30) and population PK analysis	< LEUPROLIDE DEPOT> 22.5 mg multiple dose, i.m., every 3 month	163	Patients with prostate cancer	168 days
(b) (4)					

castration of subjects within 1 month from administration with a duration of castration of 3-4 weeks.

(b) (4)

Phase 3 clinical trial GP/C/05/PRO was performed to evaluate the efficacy and safety of LUTRATE DEPOT 22.5 mg formulation in 163 prostate cancer patients. In this study, the leuprolide PK was assessed in a subset of 30 patients.

Reviewer's note: The applicant also submitted a population PK report and a sigmoid Emax model with a baseline effect parameter (E_0) using 30 patients' data in Phase 3 trial GP/C/05/PRO. Together with Dr. Liang Zhao in Division Pharmacometrics, the clinical pharmacology team decided not to review these two study reports, as the results will not affect the decision-making in this NDA submission due to small sample size.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Leuprolide acetate is a GnRH agonist indicated for prostate cancer. Plasma testosterone level is a standard biomarker that has been used to assess drug activity in prostate cancer. Achievement and maintenance of castration (the level of testosterone ≤ 0.5 ng/mL) is the primary efficacy endpoint. The plasma concentration of testosterone was measured (b) (4) by a validated LC/MS/MS assay in Trial GP/C/05/PRO.

OSIS inspection concluded that (b) (4) are acceptable (see OSIS review by Dr. Arindam Dasgupta in DARRTs).

2.2.3 Exposure-Response Relationship

2.2.3.1 Does this drug prolong the QT or QTc interval?

In the current submission, the applicant did not perform ECG monitoring or QTc prolongation evaluation. Literature suggests that androgen-deprivation therapy causes QT prolongations and it may be associated with an increased risk of cardiovascular morbidity and death. (b) (4)

2.2.4 Pharmacokinetic characteristics of the drug

2.2.4.1 What are the single dose and multiple dose PK parameters?

Please see the clinical and statistical review for the evaluation of the time course of testosterone as the primary efficacy endpoint. (b) (4)

(b) (4)

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(b) (4)

Strength 22.5 mg:

Following the first administration, plasma leuprolide concentrations increased rapidly. The peak was followed by a decline over the next several days, maintaining sustained drug levels after Day 28 until the following dose on day 84. Concentrations of leuprolide were measurable up to 84 days for 18 out of the 30 subjects. The profile of leuprolide concentrations following the second dose was similar to that following the first dose. Following the two injections of LUTRATE DEPOT 22.5 mg, there was mild accumulation of leuprolide.

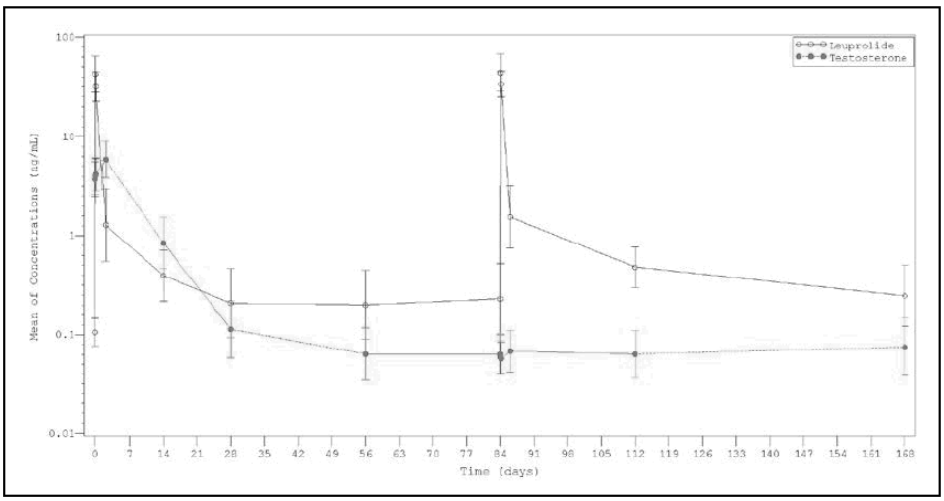

Figure 3: Plasma Leuprolide and Plasma Testosterone Concentrations

(pg/mL) (Mean ± SD) During Two Sequential I.M. Injections of LUTRATE DEPOT 22.5 mg with 3-Month Apart.

Source: [5.3.5.2. Study GP/C/05/PRO Report, Figure 11.5]

Table 4. Leuprolide Pharmacokinetic Parameters During the First Two 3-Monthly I.M. Injections of LUTRATE DEPOT 22. 5 mg (N = 30)

Day/ Dose Parameter	N	Mean	(±SD)
Day 0/ Dose 1			
C_{max} (ng/mL)	30	46.79	(18.008)
t_{max} (day)	30	0.07	(0.051)
C_{wk12} (ng/mL)	28	0.34	(0.434)
AUC_{0-t} (hr*ng/mL)	30	1696.74	(963.535)
$AUC_{0-12wks}$ (hr*ng/mL)	30	1698.40	(962.242)
$C_{avg\ 0-12wks}$ (ng/mL)	30	141.53	(80.187)
Day 84/ Dose 2			
C_{max} (ng/mL)	30	48.30	(18.557)
T_{max} (day)	30	0.08	(0.056)
C_{wk12} (ng/mL)	29	0.32	(0.285)
AUC_{0-t} (hr*ng/mL)	30	2328.84	(1134.039)
$AUC_{0-12wks}$ (hr*ng/mL)	29	2336.58	(1144.831)
$C_{avg\ 0-12wks}$ (ng/mL)	30	193.58	(93.949)

Source: [5.3.5.2. Study GP/C/05/PRO Report, Table 11.4.16]

2.2.4.2 How do the PK parameters change with time following chronic dosing?

No apparent accumulation was observed after the (b) (4) first two doses for 22.5 mg strength (Figure 3, Table 4).

2.2.4.3 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

(b) (4)

For LUTRATE DEPOT® 22.5 mg strength, the coefficient of variation (CV) is 38.4% for C_{max}, and varies from 48.5% to 56.8% for AUC following the first two doses (Table 4).

2.3 GENERAL BIOPHARMACEUTICS

2.3.1 What is the composition of the to-be-marketed formulation?

Each proposed commercial kit of the drug product LUTRATE DEPOT® (b) (4) 22.5 mg contains:

- One vial

- One prefilled syringe
- One transfer device including one sterile needle (20 gauge)
- A complete prescribing information enclosure

The vial contains sterile lyophilized microspheres of leuprolide acetate incorporated in a biodegradable polymer. (b) (4) hen mixed with 2 mL of accompanying diluent, LUTRATE DEPOT 22.5 mg for 3-month administration is administered as a single intramuscular injection EVERY 12 WEEKS.

The composition of the to-be-marketed LUTRATE DEPOT® is shown in Table 5.

Table 5. Composition of LUTRATE DEPOT® (b) (4) 22.5 mg/Vial)

INGREDIENT	QUANTITY (b) (4) LUTRATE 22.5 mg	FUNCTION	REFERENCE TO STANDARDS
Active Ingredient			
Leuprolide Acetate[2]	22.5 mg	Active Ingredient	Ph Eur*
Excipients			
(b) (4)	---	(b) (4)	In - House
PLA	(b) (4)		In - House
Triethyl citrate (TEC)			Ph Eur/USP*
Mannitol	88.4 mg		Ph Eur/USP*
Carmellose Sodium	25.0 mg		Ph Eur/USP*
Polysorbate 80	3.8 mg		Ph Eur/NF*

Source: NDA205054 Section 3.2.P.1.

2.3.2 Has the applicant developed an appropriate dissolution method and specification that will assure *in-vivo* performance and quality of the product?

Please refer to biopharmaceutical review by Dr. Sandra S. Sharp.

2.4 ANALYTICAL SECTION

2.4.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Leuprolide is the active ingredient measured for PK evaluation, and the plasma concentration of testosterone was measured as the surrogate marker for the primary efficacy endpoint.

2.4.2 For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

Total plasma concentration of leuprolide was measured. The total drug instead of free drug concentration measurement appears acceptable, as the *in vitro* binding of leuprolide to human plasma proteins was reported to range from 43% to 49%.

2.4.3 What bioanalytical methods are used to assess concentrations of leuprolide and testosterone?

(b) (4)

Strength 22.5 mg in Phase trial GP/C/05/PRO:

Leuprolide plasma concentrations were measured in patients using a validated Enzyme Immunoassay (EIA) technique. Blood was collected in 10 mL PET tubes containing 25μM PPACK, 4.5 mM EDTA) and 500 KIU/mL aprotinin, and then centrifuged (1600×g at 4°C for 15

minutes). Plasma was collected into PP tubes, divided into 2 aliquots and stored at -70°C or colder before analysis.

The characteristics of bioanalytical method are summarized below (Table 7), based on the Validation Report [redacted] (b) (4) Project Code: UX034) for 'Determination of Leuprolide in Human Plasma by EIA':

Table 7. Characteristics of the Validated Enzyme Immunoassay (EIA) Method Used to Measure Leuprolide Plasma Concentration in Trial GP/C/05/PRO

Calibrated Range	0.050 – 2.00 ng/mL
Defined LLOQ	0.100 ng/mL
Defined ULOQ	1.75 ng/mL
Inter-assay Accuracy [bias %]	Between -3.40% and 11.6%
Inter-assay Precision [CV %] (ICH: Intermediate Precision)	Between 3.70% and 11.3%
Intra-assay Accuracy [bias %]	Between -13.7% and 27.6%
Intra-assay Precision [CV %] (ICH: Repeatability)	Between 0.433% (VSULOQ 2.00 ng/mL) and 10.7%

Testosterone

Upon the request of the Division of Oncology Products 1 (DOP1), the Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the bioanalytical assays used in the measurement of testosterone concentrations [redacted] (b) (4). The OSIS inspection concluded that the bioanalytical assays used for the measurement of testosterone concentrations are acceptable. Please see OSIS review by Dr. Arindam Dasgupta in DARRTS for more information.

[redacted] (b) (4)

(b) (4)

(b) (4)

Phase 3 Study GP/C/05/PRO:

A total of 2066 human plasma samples (N= 163 patients) in Phase 3 Study GP/C/05/PRO were analyzed for the content of Testosterone according to the bioanalytical method "Quantitative Determination of Testosterone in Human Plasma by LC-MS/MS". Testosterone and the internal standard were extracted from plasma by liquid/liquid-extraction. The samples were analyzed by

LC-MS/MS using Turbo Ion Spray Ionization and Multiple Reaction Monitoring (MRM). The standard curves were linear in the measured range of 0.100 ng/mL to 10.0 ng/mL. The lower limit of quantification was 0.100 ng/mL using 0.250 mL plasma.

Table 9. Characteristics of the LC/MS/MS Method Used to Measure Testosterone Plasma Concentration in Trial GP/C/05/PRO

Validated Parameter	Results Testosterone in Human Plasma
Calibration range	0.250-10.0 ng/mL
LLOQ	0.250 ng/mL
r^2 (overall mean)	0.99810
Inter-run precision*	cv = 2.9 - 4.2%
Inter-run accuracy*	bias = 5.8%
Intra-run precision*	cv =0.8 – 2.6 %
Intra-run accuracy*	bias = 10.6%
Selectivity	no problem
Matrix test	no problem
Stability in plasma at room temperature	at least 24 h
Stability after 3 Freezing / Thawing Cycles	no problem
Stability of extracts of samples in a refrigerator (5°C ± 3°C)	at last 72 h
Stability of prepared samples at room temperature	at least 24 h
Stability of prepared samples under autosampler conditions (~10°C)	at least 72 d
Stability of prepared samples in a refrigerator (5°C ± 3°C)	at least 72 d
Stability in plasma at -20°C ± 5°C	at least 15 d
Stability of Analyte in the Stock Solution**	490 days at 5°C ± 3°C / 6 h at RT
Stability of Analyte in the Working Solution**	490 days at 5°C ± 3°C / 6 h at RT
Stability of I.S. in the Stock Solution**	496 days at 5°C ± 3°C / 6 h at RT
Stability of I.S. in the Working Solution**	15 days at 5°C ± 3°C / 6 h at RT
Recovery	79.1% (Analyt) 79.5% (IS)
Matrix Effekt	no significant effects observed
Dilution procedures	up to 4-fold

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/s/

PENGFEI SONG
04/17/2015

ELIMIKA PFUMA
04/17/2015