A Phase IV Interventional Safety Study of ELIGARD® in Prostate Cancer Patients in Asia (ELIGANT)

ISN/Protocol 7015-MA-3072

Version 2.0

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NCT03035032

Sponsor:

Astellas Pharma Singapore Pte Ltd

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I. SIGNATURES

1. SPONSOR'S SIGNATURE

Required signatures (e.g. Protocol authors, Sponsor's reviewers and contributors, etc.) are located in **Section 13, Sponsor's Signatures**; e-signatures (when applicable) are located at the end of this document.

2. INVESTIGATOR'S SIGNATURE

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines and applicable local regulations. I will also ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: .....

Date (DD MMM YYYY)

Printed Name: .....

Address: .....

.....

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

Sponsor's personnel: 24h- Contact for Serious Adverse Events (SAEs): See **Section 5.6.5**	The SAEs should be reported via eCRF (see **Section 5.6.5**). The email and fax number provided below are back-up reporting channels when the eCRF is not available: IQVIA Lifecycle Safety Email: QLS_Eligard@quintiles.com Fax: +65 6872 8462 Astellas Global Pharmacovigilance-EU Email: Safety-EU@astellas.com Fax: +31 71 545 5208
Medical Monitor:	*PPD*
Clinical Research Contacts:	*PPD*

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
ADaM	Analysis Data Model
ADT	Androgen Deprivation Therapy
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AST	Aspartate Transaminase
AT	Aminotransferase
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CRPC	Castrate Resistant Prostate Cancer
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
EAU	European Association of Urology
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EORTC	European Organization for Research and Treatment of Cancer
EQ5D-5L	EuroQol 5 Dimension 5 Level Health State Utility Index
FAS	Full Analysis Set
FDA	Food Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GnRH	Gonadotropin Releasing Hormone (synonymous to LHRH)
GPP	Good Pharmacovigilance Practice
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	Health Related Quality of Life
ICF	Informed Consent Form
ICH-GCP	International Conference on Harmonisation – Good Clinical Practice
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
KM	Kaplan-Meier
LA-CRF	Liver Abnormality Case Report Form
LDH	Lactate Dehydrogenase
LFT	Liver Function Testing
LHRH	Luteinizing Hormone Releasing Hormone (synonymous to GnRH)
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
O.D.	Once Daily

Abbreviations	Description of abbreviations
PASS	Post-Authorization Safety Study
PD	Protocol Deviation
PDAS	Pharmacodynamic Analysis Set
PET	Positron Emission Tomography
PHI	Protected Health Information
PKAS	Pharmacokinetic Analysis Set
pPRO	Paper Patient Reported Outcome
PPS	Per Protocol Set
PS	Pre-Screening
PRO	Patient Reported Outcome
PSA	Prostate Specific Antigen
PT	Preferred Term
QC	Quality Control
QLQ	Quality of Life Questionnaire
QoL	Quality of Life
RFT	Renal Function Test
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SOP	Standard Operating Procedures
TBL	Total Bilirubin
TMF	Trial Master File
TNM	Tumor, Nodes, Metastasis
ULN	Upper Limits of Normal
VAS	Visual Analogue Scale
WD	Withdrawal
WHO	World Health Organization
WMA	World Medical Association

Definition of Key Study Terms

Terms	Definition of terms
Adverse Event (AE)	An adverse event is as any untoward medical occurrence in a patient administered a study drug and which does not necessarily have a causal relationship with this treatment *(see also Eligard-related AE)*.
Approval (in relation to IRB)	The affirmative decision of the institutional review board (IRB) that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, good clinical practice (GCP), and the applicable regulatory requirements.
Baseline	1. Observed values/findings which are regarded as starting points for comparison. 2. Time when 'Baseline' is observed.
Case Report Form (CRF)	A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor for each trial patient.
Castrate Resistant Prostate Cancer (CRPC)	The European Association of Urology (EAU) Prostate Cancer Guidelines 2016 defines CRPC as: Castrate serum testosterone < 50ng/dL or 1.7 nmol/L plus either; Biochemical progression: 3 consecutive rises in prostate specific antigen (PSA) at least 1 week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL or Radiological progression: the appearance of two or more new bone lesions on bone scan or enlargement of a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumors). Symptomatic progression alone must be questioned and is not sufficient to diagnose CRPC.
Causality Assessment	An evaluation performed by a medical professional concerning the likelihood that a therapy or product caused or contributed to an AE. A positive causality assessment made by either reporter and/or company makes an AE into an ADR.
Clinical Study	Any investigation in relation to humans intended: a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of 1 or more medicinal products; b) to identify any adverse reactions to 1 or more medicinal products; or c) to study the absorption, distribution, metabolism and excretion of 1 or more medicinal products; with the objective of ascertaining their safety or efficacy.
Confidence Interval (CI)	A measure of the precision of an estimated value. The interval represents the range of values, consistent with the data that is believed to encompass the "true" value with high probability (usually 95%) upon repeated sampling according to frequentist theory. The confidence interval (CI) is

	expressed in the same units as the estimate. Wider intervals indicate lower precision; narrow intervals, greater precision.
Confidentiality	Prevention of disclosure to other than authorized individuals of proprietary information or of a patient's identity.
Consent Form	Document used during the informed consent process that is the basis for explaining to potential patients the risks and potential benefits of a study and the rights and responsibilities of the parties involved. The informed consent document provides a summary of a clinical trial (including its purpose, the treatment procedures and schedule, potential risks and benefits, alternatives to participation, etc.) and explains an individual's rights as a patient. It is designed to begin the informed consent process, which consists of conversations between the patient and the research team. If the individual then decides to enter the trial, s/he gives her/his official consent by signing the document. Synonym: informed consent form (ICF)
Contract Research Organization (CRO)	A person or an organization (commercial, academic, or other) contracted by the sponsor to perform 1 or more of a sponsor's trial-related duties and functions.
Data Collection	In the context of clinical research, accessing and recording information that provides source data for analysis and interpretation.
Data Management	Tasks associated with the entry, transfer, and/or preparation of source data and derived items for entry into a clinical trial database. Data management could include database creation, data entry, review, coding, data editing, data quality control (QC), locking, or archiving; it typically does not include source data capture.
Data Monitoring	Process by which data are examined for completeness, consistency, and accuracy.
Data Quality	A dimension of data contributing its trustworthiness and pertaining to accuracy, sensitivity, validity, and suitability to purpose. Key elements of data quality include attribution, legibility (decipherable, unambiguous), contemporaneousness, originality (i.e., not duplicated), accuracy, precision, completeness, consistency (logical, not out of range), and those who have modified the data.
Declaration of Helsinki	A set of recommendations or basic principles developed by the World Medical Association (WMA) that guide medical doctors in the ethical conduct of biomedical research involving human patients. It was originally adopted by the 18th World Medical Assembly (Helsinki, Finland, 1964).
Demographic data	Characteristics of patients or study populations, which include such information as age, sex, family history of the disease or condition for which they are being treated, and other characteristics relevant to the study in which they are participating.

Discontinuation	The act of concluding participation, prior to completion of all protocol-required elements, in a study by an enrolled patient.
Effectiveness	The capability of an intervention in producing a desired result under circumstances that more closely approach real-world practice, with more heterogeneous populations, less-standardized treatment protocols, and delivery in routine clinical settings.
Electronic Case Report Form (eCRF)	Auditable electronic record designed to capture information required by the clinical trial protocol to be reported to the sponsor on each trial patient.
Eligard-related Adverse Event	An adverse event in a patient administered Eligard where a causal relationship is at least a reasonable possibility (drug event with either a possible or probable causal relationship), as determined by the opinion of the investigator. Adverse events listed in the local label should be used by the investigator as reference safety information to understand whether an adverse event is expected with the use of Eligard. This understanding should inform causality assessments by the investigator.
Ethnic Asian	Any of the following races - Chinese, Filipino, Indonesian, Malay, Thai, Vietnamese, Indian, Japanese or Korean.
Final Visit	The final visit will be the same as the last follow-up visit for each patient. It will occur at the 18th month after enrollment into the study, provided that none of discontinuation criteria (see **Section 6**) are met.
Hormonal Treatment-Naive Prostate Cancer	Prostate cancer that has not received endocrine manipulation.
Hormone Sensitive Prostate Cancer	Prostate cancer that has been treated with hormonal agents but has not progressed.
Patient Reported Outcome (PRO)	A PRO is a measurement based on a report that comes from the patient (i.e., study patient) about the status of a patient's health condition without amendment or interpretation of the patient's report by a clinician or anyone else. A PRO can be measured by self-report or by interview, provided that the interviewer records only the patient's response. Symptoms or other unobservable concepts known only to the patient (e.g., pain severity or nausea) can only be measured by PRO measures. PROs can also assess the patient perspective on functioning or activities that may also be observable by others.
Post-Authorization Safety Study (PASS)	Any study relating to an authorized medicinal product in the EU, conducted with the aim of identifying, characterizing, or quantifying a safety hazard (e.g., a potential or identified risk), confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures [DIR 2001/83/EC Art 1(15)/ GVP Module VIII]. A post-authorization safety study may be an interventional clinical trial or may follow a non-interventional study design.
Primary data collection	Data collection directly from patients and healthcare professionals.
Protocol	A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually

	also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the International Conference on Harmonisation – Good Clinical Practice (ICH GCP) Guideline the term protocol refers to protocol and protocol amendments.
Quality of Life (QoL)	A broad ranging concept that incorporates an individual's physical health, psychological state, level of independence, social relationships, personal beliefs, and their relationships to salient features of the environment. Note: Quality of Life is one way to measure the benefits or negative impacts of an "improvement" measured in terms of a physiological or psychological symptom. QoL research seeks to quantify what an intervention means to a patient's sense that their life has changed.
Questionnaire	A set of questions or items shown to a respondent in order to get answers for research purposes.
Safety	Relative freedom from harm. In clinical trials, this refers to an absence of harmful side effects resulting from use of the product and may be assessed by laboratory testing of biological samples, special tests and procedures, psychiatric evaluation, and/or physical examination of patients.
Sample Size	A subset of a larger population, selected for investigation to draw conclusions or make estimates about the larger population.
Serious Adverse Event (SAE)	An SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution. An SAE must fulfill at least 1 of the following criteria at any dose level: results in death; is life threatening, results in persistent or significant disability/ incapacity or substantial disruption of the ability to conduct normal life functions; results in congenital anomaly, or birth defect; requires inpatient hospitalization or leads to prolongation of hospitalization; or a medically important event.
Serious Eligard-related Adverse Event	An Eligard-related AE which results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/ incapacity, is a congenital anomaly/ birth defect, or results in other medically important events. Adverse events listed in the local label should be used by the investigator as reference safety information to understand whether a serious adverse event is expected with the use of Eligard. This understanding should inform causality assessments by the investigator
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Statistical Analysis Plan (SAP)	A document that contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.
Statistical Method	The particular mathematical tests and techniques that are to be used to evaluate the clinical data in a trial.
Study Period	Period of time from the initiation date to the completion date of the study.
Study Population	Defined by protocol inclusion/exclusion criteria.
Visit	A clinical encounter that encompasses planned and unplanned trial interventions, procedures, and assessments that may be performed on a patient. A visit has a start and an end, each described with a rule.
Withdrawal	The act of discontinuing participation in a clinical study. *See also discontinuation.*

IV. SYNOPSIS

Date and Version # of Protocol Synopsis:	18 APR 2018 version 2.0
Sponsor: Astellas Pharma Singapore Pte Ltd 6 Temasek Boulevard, #26-03/04/05 Suntec Tower Four, Singapore 038986	**Protocol Number:** 7015-MA-3072
Name of Study Drug: Leuprorelin acetate (ELIGARD®) 22.5mg (subcutaneous injection every 3 months)	**Phase of Development:** Phase 4
Title of Study: A Phase IV Interventional Safety Study of ELIGARD® in Prostate Cancer Patients in Asia (ELIGANT)	
Planned Study Period: From Q2 2017 to Q1 2020 Start of data collection: Q2 2017 End of data collection: Q1 2020 Final report of study results: Q3 2020 Publication: Q3 2021	
Study Objective(s): The objectives of this Phase IV, prospective, interventional study are to evaluate the safety, efficacy, and impact on quality of life (QoL) of ELIGARD® in hormone-dependent prostate cancer patients in Asia. Primary Objective: To establish the safety profile of ELIGARD® in ethnic Asian prostate cancer patients Secondary Objectives: (i) To describe the efficacy of ELIGARD® 22.5 mg (3-monthly formulation) in controlling prostate specific antigen (PSA) and testosterone levels (ii) To assess health-related quality of life (HRQoL) through QoL questionnaires – European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-PR25) (prostate cancer disease specific patient reported outcome [PRO]) and EuroQol 5 Dimension 5 Level Health State Utility Index (EQ5D-5L) (generic PRO)	
Planned Total Number of Study Centers and Location(s): Approximately 20 centers in 8 Asian Countries	
Study Population: This study is designed for male patients with: • Locally advanced prostate cancer with biochemical relapse following radical prostatectomy and/or radiotherapy (see inclusion criteria 4) • Hormonal treatment-naive advanced or metastatic prostate cancer	
Number of Patients to be Enrolled: 107 to be entered.	

Study Design Overview:
This is a multicenter, prospective, single-arm, interventional study of male patients with prostate adenocarcinoma who fulfill the eligibility criteria.

The planned total duration of this study is 30 months from the date that the first patient is enrolled until 3 months after the last dose of ELIGARD® 22.5 mg administration. The enrollment period will be up to 12 months. Patients will be treated for 1.5 years (18 months), with ELIGARD® 22.5 mg being administered at baseline, 3rd month, 6th month, 9th month, 12th month and 15th month. Adverse Event (AE) and Serious Adverse Event (SAE) collection will start at baseline until the follow-up visit at 18 months. QoL will be measured at baseline, 6th month, 12th month and 18th month. The PSA and testosterone will be assessed at all scheduled visits. Patients will be followed up to 18th month in the physician's office. Any other assessments including imaging tests are not mandatory and will be performed according to routine standard of care and physician's discretion.

Inclusion/Exclusion Criteria:
A patient is eligible for the study if he meets all of the inclusion criteria and none of the exclusion criteria:

Inclusion:
A patient for whom the physician has decided to initiate treatment with a Luteinizing Hormone Releasing Hormone (LHRH) agonist in standard clinical practice will be approached for enrolment into this study.

1. Ethnic Asian male patient above 18 years of age
2. Willing and able to provide written informed consent
3. Biopsy-proven prostate adenocarcinoma
4. Locally advanced prostate cancer with biochemical relapse following radical prostatectomy and/or radiotherapy. Biochemical relapse [Mottet et al, 2006] is defined as:
    - PSA > 2 ng/mL following radiotherapy, or
    - Two consecutive PSA values > 0.2 ng/mL and rising above the nadir following radical prostatectomy

    OR

    Hormonal treatment-naive advanced or metastatic prostate cancer patient who has not received chemotherapy and has no plans to undergo treatment with chemotherapy at study entry.
5. Patient who indicates that once the study is completed, he expects having access to androgen deprivation therapy (ADT), either medical or surgical, within the local healthcare system (either through public/ private health insurance or out of pocket payment).

Exclusion:

1. Patient with castrate resistant prostate cancer (CRPC)
2. Patient who previously underwent bilateral orchiectomy
3. Patient who has received prior treatment with LHRH analogues
4. Prior or concomitant treatment with systemic chemotherapy. A patient where there is a likelihood to receive systemic chemotherapy should not be enrolled
5. Life expectancy of < 1 year due to comorbidities
6. Participation in another interventional clinical trial within 1 month prior to study entry or during the duration of the study
7. Physician is planning to give the patient intermittent ADT at the time of study entry
8. Patient receiving non-palliative radiotherapy within 3 months prior to study entry
9. Patient receiving adjuvant ADT in combination with definitive radiotherapy
10. Patient with metastatic hormonal treatment-naive prostate cancer, for whom chemo-hormonal treatment (combination of Docetaxel and ADT) is indicated.
11. Patient with hypersensitivity to gonadotropin releasing hormone (GnRH), GnRH agonist analogs or any of the components of ELIGARD®
12. Patient with any contraindication for ELIGARD® use based on local prescribing information

Investigational Product(s):
ELIGARD® 22.5mg
Note: ELIGARD® will be provided by the Sponsor during the conduct of this study.

Dose:
ELIGARD® 22.5mg (1 depot injection every 3 months)

Mode of Administration:
Subcutaneously

Comparative Drug(s):
Not applicable as this is a single arm interventional study of ELIGARD®.

Dose(s):
Not applicable

Mode of Administration:
Not applicable

Concomitant Medication Restrictions or Requirements:
Bicalutamide 50 mg once daily (O.D.) or similar anti-androgen is an allowed concomitant medication for flare prevention only.
The anti-androgen for flare prevention should be considered beginning at least 3 days to 4 weeks prior to the first ELIGARD® injection and continuing for the first 2 to 3 weeks of treatment. This has been reported to prevent the sequelae of an initial rise in serum testosterone. Use of bicalutamide or a similar anti-androgen beyond 3 weeks after starting ELIGARD® therapy and for reasons other than flare prevention is not allowed.
Note: Anti-androgens will not be provided by the Sponsor.

List of Excluded Concomitant Medications:

1. Other LHRH analogues,
2. LHRH antagonists and other agents (approved or investigational) which are known to impact on testosterone or PSA level,
3. Ketoconazole,
4. Estrogens,
5. Herbal medications that may affect PSA levels (i.e., saw palmetto),
6. Androgens (testosterone, dihydroepiandrosterone, etc.),
7. Abiraterone,
8. Enzalutamide,
9. Chemotherapy agents including docetaxel and platinum drugs

Duration of Treatment:
The planned total duration of this study is30 months from the date the first patient is enrolled until 3 months after the last dose of ELIGARD® 22.5 mg administration. The enrollment period will be up to 12 months. ELIGARD® 22.5 mg will be administered at baseline, 3 months, 6 months, 9 months, 12 months and 15 months. Patients will be followed up at 18 months in the physician office.

At the 18th month or last visit, treatment with ELIGARD® or other alternatives as deemed appropriate by the investigator may be continued. ELIGARD® or other alternatives will not be provided after the 15th month dose. Treatments administered after the 15th month or last visit, not limited to LHRH analogues, will be at the investigator's discretion and such data will not be collected.

Formal Stopping Rules:
The trial will be closed 18 months after the end of the enrollment period (3 months after the last dose of ELIGARD® 22.5 mg has been administered).

Endpoints for Evaluation:
Primary:
ELIGARD®-related adverse events (AEs) throughout the entire observation period, as determined by the opinion of the investigator

Secondary:

- Efficacy outcomes of clinical response based on testosterone and PSA levels (Testosterone and PSA will be assessed for all patients at each scheduled visit, prior to administering ELIGARD®, and at the follow up visit.)
- HRQoL assessment through QoL questionnaires – EORTC QLQ-PR25 (prostate cancer disease specific patient reported outcome [PRO]) and EQ5D-5L (generic PRO) measured at 0, 6, 12, and 18 months.

Statistical Methods:

Sample size justification:
This study targets to enroll approximately 107 prostate cancer patients.
The sample size was calculated based on the estimated percentage of ELIGARD®-related AEs, as well as the desired width of its 95% Confidence Interval (CI). Prior clinical studies on ELIGARD® have shown that around 50% of patients experience ELIGARD®-related AEs during a 6-month treatment period. With the assumption that the percentage of ELIGARD®-related AEs will be 50%, a sample size of 96 completed patients is sufficient for estimating a Wald 95% CI with a width of 20% (+/- 10% from the middle), based on a finite population correction, with factor N=10,000.
Therefore, total sample size of this study, assuming a drop-out rate of 10%, is 107 patients.
PASS 14 Power Analysis and Sample Size Software (2015) version number 14.0.2 was used in the sample size calculation.

Safety:
Safety is the primary endpoint. The safety analysis is based on the occurrence of ELIGARD® related AEs and ELIGARD®-related SAEs throughout the entire observation period and physician's assessment of overall drug safety. All AEs and SAEs, independent of investigator assessed causality, occurring during the study will be collected and summarized by Preferred Term (PT) and categorized by System Organ Class (SOC), severity and relationship to ELIGARD®. The modification of treatment in response to AEs will be described where appropriate. The safety analysis set (SAF) consists of all patients enrolled in the study for whom there is evidence of ELIGARD® study medication use and for whom any follow-up safety information is available.

ELIGARD®-related AEs and SAEs will be summarized according to their severity, grade using the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Event (CTCAE) guidelines, outcome, course of event, seriousness, action taken with ELIGARD® and treatment required to manage the AE. Incidence rates of ELIGARD®-related AEs and SAEs will be presented using descriptive statistics and a 95% 2-sided CI. In addition, Kaplan Meier (KM) estimates will be used to summarize median time to first related AE, incidence rates at each scheduled time-point as well as a visual support to present time-to-event trends. Summaries of ELIGARD®-related AEs and SAEs which occur after receiving CRPC management will be presented separately.

Efficacy:

Primary efficacy variable:

Not applicable. The primary analysis of this study is a safety analysis.

Secondary efficacy variables

- Percentage of patients with Testosterone <20, 20-50 and >50 ng/dL at 1 year and at 1.5 years
- Time to PSA progression: calculated from date of first administration of ELIGARD® 22.5 mg to PSA progression
- PSA progression will be defined as a 25% or greater increase and an absolute increase of 2 ng/mL or more from the nadir is documented, which is
    - Confirmed by a second value obtained 3 or more weeks later
    - If not done based on standard clinical practice, the confirmatory PSA measurement will be performed at the next routine study visit.

  Note: The aim is to detect time to PSA progression and not to assess whether the patient has progressed to CRPC. Imaging and other modalities should be used to determine if the patient has moved to CRPC, which is outside the scope of this study.
- HRQoL using EQ5D-5L questionnaire and QLQ-PR25 prostate cancer questionnaire

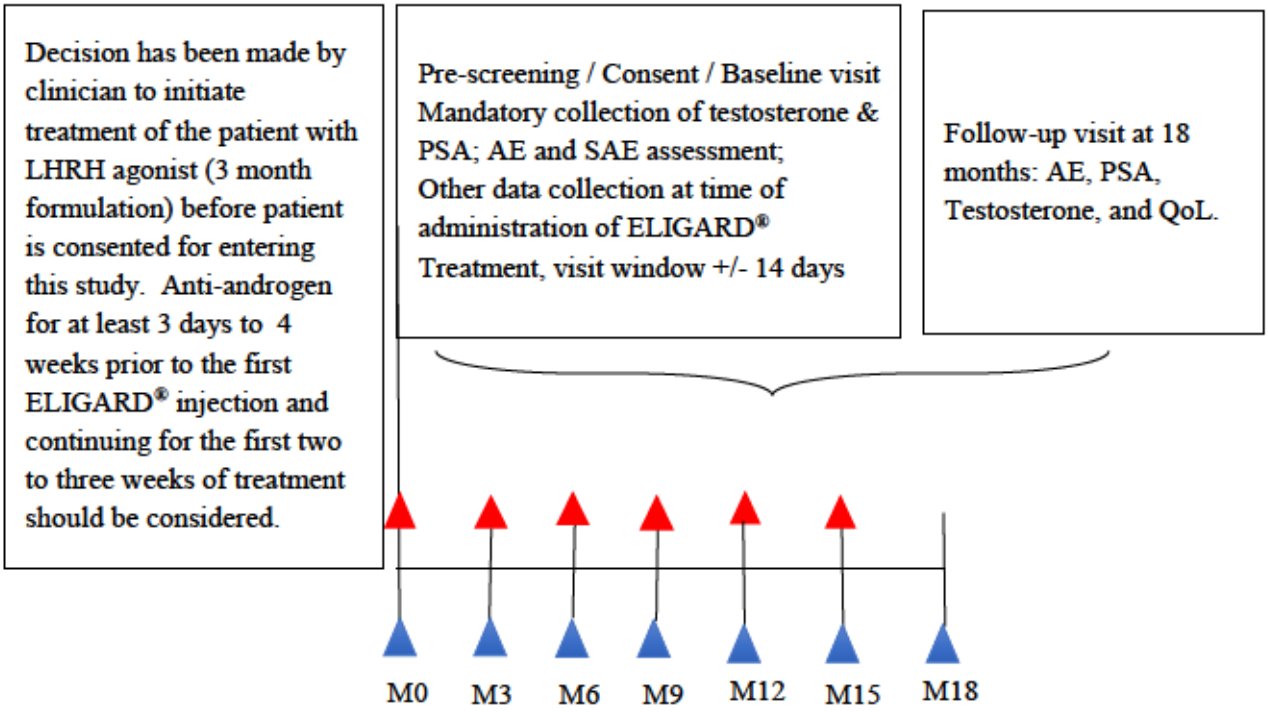
Pharmacokinetics: Not applicable

Pharmacodynamics: Not applicable

Interim analyses:
A minimum of 1 interim analysis will be conducted when 50 patients complete 1 year of follow-up. As there are no statistical hypothesis tests in the planned analysis, the conduct of interim analyses will not have any statistical implications on the final study outcome.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart



Legend:

Administration of ELIGARD®, details are listed in #.

Data Collection Points

Notes:

#: ELIGARD® will be administered at baseline, 3 months, 6 months, 9 months, 12 months, and 15 months. PSA and Testosterone levels to be measured in all the visits. Visit window is +/- 14 days. QoL to be measured at baseline, 6 months, 12 months and 18 months. Any other assessments including imaging tests are not mandatory and will be performed according to routine standard of care and physician's discretion. One month = 30 days.

Table 1: Schedule of Assessments

		ELIGARD® 22.5 mg treatment						Early withdrawal [m]	Follow up visit [n]
	Pre-Screening	Baseline	Month 3	Month 6	Month 9	Month 12	Month 15	WD	Month 18
Day/Month	PS	0	3	6	9	12	15	WD	18
Visit Number		1	2	3	4	5	6		7
Time Windows (days)			+/- 14	+/- 14	+/- 14	+/- 14	+/- 14		+/- 14
STUDY MEDICATION									
ELIGARD® 22.5 mg 3-month depot		X	X	X	X	X	X		
ASSESSMENTS									
Physician-determined eligibility for ELIGARD® 22.5 mg 3-month depot	X								
Patient expectation of access to ADT post-study[a]	X								
Informed Consent (mandatory)		X							
Inclusion/ Exclusion Criteria		X							
Allocation of Patient Number		X							
Demographic Data[b]		X							
Vital Status [c]		X	X	X	X	X	X	X	X
Baseline disease characteristics for prostate cancer [d]		X							
Medical History [e]		X							
Prostate Cancer Status [f]		X	X	X	X	X	X		X
Family History for Prostate Cancer		X							
ELIGARD® Use [g]		X	X	X	X	X	X		
Most important factors for selection of treatment (Rising PSA after definitive treatment, optimal testosterone control, quality of life, convenience of 3-monthly formulation, other).		X							
Details on supportive care (including type of treatment, drug dose, schedule & duration) or supportive care measures, including other concomitant		X	X	X	X	X	X		X

		ELIGARD® 22.5 mg treatment						Early withdrawal [m]	Follow up visit [a]
	Pre-Screening	Baseline	Month 3	Month 6	Month 9	Month 12	Month 15	WD	Month 18
Day/Month	PS	0	3	6	9	12	15	WD	18
Visit Number		1	2	3	4	5	6		7
medications related to cancer (e.g. pain medications, bone protective medications, spinal cord decompression surgery, palliative radiotherapy etc.)									
Reasons for discontinuation of ELIGARD® including AEs		X	X	X	X	X	X	X	X
AEs and SAEs Assessment [h]		X	X	X	X	X	X	X	X
Treatment for AEs and SAEs		X	X	X	X	X	X	X	X
PSA level, date and methods of test [i]		X	X	X	X	X	X		X
Serum testosterone level, date and methods of test [j]		X	X	X	X	X	X		X
Other laboratory Tests (if done within routine practice, last available value that is closest to each visit) [j]		X	X	X	X	X	X		X
Tumor evaluation/ Radiographic assessments and date of test [k]		X	X	X	X	X	X		X
Concomitant Medications Assessment		X	X	X	X	X	X	X	X
EORTC QLQ-PR25 (to be measured at baseline, 6 months, 12 months and at 18 months, mandatory) [l]		X		X		X			X
EQ5D-5L (to be measured at baseline, 6 months, 12 months and 18 months mandatory) [l]		X		X		X			X

Legend: X – required by protocol or if available in patient charts based on routine clinical practice. WD: withdrawl.
Footnotes:

[a] The assessment of patient's access to medical or surgical androgen deprivation therapy after the trial ends will be based on the interview by the physician at prescreening visit.

[b] Demographic data - Date of birth (or age, if local regulations do not allow recording of patient's date of birth), Race as described by the patient (unless local regulations do not allow recording of patient's race), highest education level

[c] Vital status – blood pressure, pulse rate, respiratory rate and weight. Height to be collected at baseline visit only

[d] Baseline disease characteristics for prostate cancer - Time since diagnosis, Gleason score at initial diagnosis, Tumor, Nodes, Metastasis (TNM) classification, surgical history, biopsy results, dates and types of anti-neoplastic therapy including radiation therapy prior to study inclusion (including number of cycles, treatment duration, time interval since previous treatments), Eastern Cooperative Oncology Group (ECOG) status, bone lesions, soft tissue disease, visceral disease, pain.

[e] Medical history – diabetes, hypertension, cardiac disorders

[f] Prostate cancer status - stage of prostate cancer, bone metastasis, soft tissue disease, visceral disease, pain (using Visual Analogue Scale [VAS] 0-10 which will only be collected if done in routine clinical practice), ECOG status

[g] ELIGARD® Use - ELIGARD® initiation and cessation.

[h] Adverse Events and Serious Adverse Events Assessment

- Adverse Events (AEs)
- Serious Adverse Events (Serious AEs) must be reported to the sponsor/ designee within 24 hours.
- For this study, an ELIGARD® -related AE is defined as an adverse event in a patient administered ELIGARD® where a causal relationship is at least a reasonable possibility (drug event with either a possible or probable causal relationship), as determined by the investigator. Adverse events listed in the local label should be used by the investigator as reference safety information to understand whether an adverse event is expected with the use of ELIGARD®. This understanding should inform their causality assessments.

[i] Prostate specific antigen (PSA) and Testosterone levels will be tested for all patients before ELIGARD® injection at each of the following visits: baseline, 3 months, 6 months, 9 months, 12 months, 15 months and at the follow up visit at 18 months. PSA progression must be confirmed by a second value obtained 3 or more weeks later. If PSA confirmation is not done based on standard clinical practice, the confirmatory PSA measurement will be performed at the next routine study visit.

[j] Other laboratory tests (if done within routine clinical practice, last available value that is closest to each visit will be recorded) – Lactate Dehydrogenase (LDH), Alkaline Phosphatase (ALP), Hematology, Liver Function Test (LFT) and Renal Function Test (RFT)

[k] Tumor Evaluation/Radiographic Assessments (if data available) – Computerized Tomography (CT) scan, Positron Emission Tomography (PET) Scan, Magnetic Resonance Imaging (MRI), Bone scan, X-ray, ultrasound or any other imaging test

[l] European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-PR25) and EuroQol 5 Dimension 5 Level Health State Utility Index (EQ5D-5L) – to document whether completion of questionnaires was accomplished through self-administration or through the assistance of another person

[m] A patient who discontinues from the study for whatever reason should have a follow up visit that will occur 3 months after the last administration of ELIGARD® for safety assessment. A patient that is unable to comply will be considered as a protocol deviation, provided that the reason for discontinuation is not due to patient's withdrawal of consent.

[n] The final visit and the last follow-up visit will be the same for each patient. It will occur at 18 months after enrollment, provided that none of discontinuation criteria are met.

1 INTRODUCTION

1.1 Background

Epidemiology of Prostate Cancer

Prostate cancer (PC) is the second most common malignancy in men with nearly 1 million new cases being diagnosed worldwide [Baade et al, 2013]. The analysis of GLOBOCAN data showed that more developed countries have much greater 5-year prevalence and incidence rates than underdeveloped countries [Crawford, 2003].

Approximately 14% of all prostate cancers diagnosed worldwide in 2008 were within the Asia-Pacific region. Differences in prostate cancer incidence rates and prevalence rates exist both regionally within Asia and between Asia and Western nations. The reported incidence of prostate cancer among all cancers affecting men in Asia varies by country; prostate cancer is the third most commonly diagnosed male cancer in Singapore and Malaysia, fourth in Japan and Thailand, fifth in South Korea, sixth in China, and ninth in India [Crawford, 2003]. The overall incidence of, and mortality from, prostate cancer in Asian countries are lower than the rates observed in cohorts of migratory Asians in Western countries, and considerably lower than those in native Western individuals. However, there is an increase in prostate cancer incidence in the Asia-Pacific region, where Hong Kong and Singapore (Chinese population only) recorded annual increases of around 6% for males of all ages between 1998-2009 and 1980-2002, respectively [Baade et al, 2013]. Smaller, but still significant, increases in prostate cancer incidence rates were found for males of all ages in the Philippines and Thailand (3% per year increase between 1983-2002 and 1983-2009, respectively) [Baade et al, 2013].

Prostate cancer is the most common cancer in elderly males. The incidence rates of prostate cancer increase with age. It is relatively rare for prostate cancer to be diagnosed in men <50 years of age, but after this age, the incidence and mortality rates increase exponentially [Baade et al, 2013]. In some Asian countries (Japan, Hong Kong and South Korea) the increase was more pronounced after 60 years of age [Baade et al, 2013]. The majority of cancer cases are diagnosed between 50-79 years of age [Baade et al, 2013].

Prostate cancer rates are highest in Western countries and lowest in Asian countries [Sim & Cheng, 2005]. However, Asian populations generally have higher proportions of men with advanced stage prostate cancer compared with Western populations, despite overall reports of prostate cancer incidence being substantially lower in the former [Ito, 2014]. The epidemiological pattern of prostate cancer in Asia suggests that prostate cancer often goes unnoticed, at least until later stages of the disease, possibly owing to restricted access to screening programs and urology clinics in Asian countries [Ito, 2014].

There was a large disparity in the survival prospects on men with prostate cancer throughout the Asia-Pacific region. Five-year relative survival estimates of 85% and above were reported in New Zealand, Australia, Japan, Singapore and South Korea [Baade et al, 2013]. This contrasts with estimated 5-year survival rates of between 30% to 40% in parts of China and Thailand [Baade et al, 2013].

With the expected increases in life expectancy of men and in the incidence of prostate cancer [Center et al, 2012], the disease's economic burden is also expected to increase substantially. In Europe, it is estimated that the total economic costs of prostate cancer exceed €8.43 billion, with a high proportion of the costs of prostate cancer care occurring in the first year after diagnosis [Mottet et al, 2006]. In European countries with available data (United Kingdom, Germany, France, Italy, Spain, Netherlands), this amounted to €106.7 – 179.0 million for all prostate cancer diagnosed in 2006 [Mottet et al, 2006].

In Asia, the population over 60 years old is about 4 times greater compared to those of North America and Europe [Zhang et al, 2011]. Given that life expectancy is expected to increase markedly in many parts of Asia over coming years, the burden of prostate cancer in this region is likely to increase in the future. Health problems will become a greater burden in Asian countries despite rapid socioeconomic growth.

It has been reported that patients with terminal prostate cancer show considerably decreased quality of life (QoL) for many years before death, owing to the adverse effects of long-term systemic treatments as well as physiological and psychological impairment resulting from progression of local disease and distant metastases [Ito, 2014].

ELIGARD® (leuprolide acetate for injection)

ELIGARD® (leuprolide acetate) is an established luteinizing hormone releasing hormone (LHRH) agonist that is indicated for the palliative treatment of advanced prostate cancer [ELIGARD local prescribing information, May 2014]. ELIGARD® is a long-acting depot formulation that uses Atrigel® delivery system (a biodegradable polymer matrix) that allows sustained release of leuprolide acetate following subcutaneous injection. ELIGARD® is designed to deliver leuprolide acetate at a controlled rate over a therapeutic period to reduce testosterone levels in men with advanced hormone-dependent prostate cancer. ELIGARD® is available in 3 depot formulations of 7.5 mg, 22.5 mg and 45 mg doses for 1-monthly, 3-monthly and 6-monthly administration intervals, respectively.

Study Rationale

Both the safety and efficacy of ELIGARD® have been well proven in numerous clinical studies. However, the safety profile of ELIGARD® was not established in ethnic Asian populations as no clinical studies of ELIGARD® have been conducted in Asia to date. Since data from controlled clinical trials may not necessarily be assumed to apply in their entirety to subpopulations not

studied in those trials, Astellas will conduct this study to establish the safety profile and to confirm the efficacy of ELIGARD® in prostate cancer patients in the Asia region. This study will also aim to assess health-related quality of life (HRQoL) of prostate cancer patients using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-PR25, prostate cancer disease specific patient reported outcome [PRO]) and EuroQol 5 Dimension 5 Level Health State Utility Index (EQ5D-5L, generic PRO).

This study is a non-mandated Post-authorization safety study (PASS).

1.2 Non-clinical and Clinical Data

Non-clinical data

In all animal studies, serum testosterone was suppressed below or near the castrate threshold (50 ng/dl) within 1 to 3 weeks after a single administration of ELIGARD®. Following a single administration, the duration of testosterone suppression to below castrate threshold was > 91 days with ELIGARD® 22.5 mg.

Pharmacokinetic studies with ELIGARD® 22.5 mg established near complete release of leuprorelin acetate by Day 106. Two of 3 studies with ELIGARD® 22.5 mg suggest that a smaller proportion of the total leuprorelin dose is released initially (i.e., 19 - 41% and 22%, respectively).

In single-dose toxicity studies, no untoward systemic or clinical effects (except for the desired pharmacodynamic outcome) have been observed for ELIGARD®. Similarly, repeated administration of ELIGARD® is not associated with overt toxicity other than that related to the pharmacological action of the active ingredient, leuprorelin acetate.

No acute systemic effects were observed in any of the studies performed with the delivery system (with or without leuprorelin acetate), following single-dose or repeated administration. However, in a chronic toxicity study with ELIGARD® 22.5 mg (LEU_PTX_0220), the delivery system control was found to cause mild histopathological lesions in the testis, the epididymis, the prostate, and the coagulating gland as observed with the test article, which were exaggerated when the active product was given at the high dose level (500 µl/kg, i.e., 100 times the human clinical dose).

Details of preclinical data are summarized in the ELIGARD® Investigator's Brochure, Edition 5, dated 26th June 2008 and the approved Summary of Product Characteristics.

Clinical data

Response to ELIGARD® should be monitored by measuring serum concentrations of testosterone and prostate specific antigen (PSA) periodically [ELIGARD local prescribing information, May 2014]. Majority of patients have increased testosterone levels above baseline during the first week, declining thereafter to baseline levels or below by the end of the second or third week

[ELIGARD local prescribing information, May 2014]. The patients generally achieve testosterone 'castration levels' (< 50 ng/dL) within 2 to 6 weeks after the start of ELIGARD® treatment, and the effects are reversible upon discontinuation of drug therapy [ELIGARD local prescribing information, May 2014].

Furthermore, up to 98% of patients showed levels which are less than 20 ng/ dL, comparable to those resulting from surgical bilateral orchidectomy [Berges & Bello, 2006]. This is clinically important because low serum testosterone (<20 ng/dL) within the first year of Androgen Deprivation Therapy (ADT) has been suggested to correlate with improved survival and duration of response to androgen deprivation in men being treated with ADT [Klotz et al, 2015]. The European Association of Urology Guidelines for Prostate Cancer acknowledges that better results are repeatedly observed with lower testosterone levels compared to 50 ng/dL[Mottet et al, 2006]. As with other gonadotropin releasing hormone (GnRH) agonists, ELIGARD® 22.5 mg causes a transient increase in serum concentrations of testosterone (also known as 'tumor flare' or 'testosterone surge') during the first week of treatment [ELIGARD local prescribing information, May 2014]. Patients may experience worsening of symptoms or onset of new signs and symptoms during the first few weeks of treatment, including bone pain, neuropathy, hematuria or bladder outlet obstruction [ELIGARD local prescribing information, May 2014]. Potential exacerbations of signs and symptoms of the disease in patients with vertebral metastases and/or urinary obstruction or hematuria, may lead to neurological problems such as weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms [ELIGARD local prescribing information, May 2014]. Patients at risk should be closely monitored during these first 2 weeks of therapy and managed as appropriate. Short term anti-androgen therapy may ameliorate these symptoms.

The safety of all ELIGARD® formulations was evaluated in clinical trials involving patients with advanced prostate cancer. The most commonly reported adverse reactions are hot flashes, nausea, malaise and fatigue and transient local irritation at the site of injection. Mild hot flashes occur in approximately 58% of patients[ELIGARD 22.5 mg, Summary of Product Characteristics 2015]. Hyperglycemia, an increased risk of developing diabetes and cardiovascular diseases such as myocardial infarction, sudden cardiac death and stroke have been reported in men receiving GnRH agonists [ELIGARD local prescribing information, May 2014]. It is important to monitor patients' blood glucose level and cardiovascular condition and manage according to current clinical practice. Decreased bone density and rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported during post-marketing experience after the administration of GnRH agonists [ELIGARD local prescribing information, May 2014]. Convulsions and QT prolongation have also been reported in the post-marketing setting [ELIGARD local prescribing information, May 2014].

ELIGARD® is contra-indicated in patients with hypersensitivity to GnRH, GnRH agonists or any of the components of ELIGARD® [ELIGARD local prescribing information, May 2014].

The pre-clinical and clinical data are summarized in the ELIGARD® Investigator's Brochure, Version 5, dated 26 June 2008 [ELIGARD Investigator's Brochure, June 2008] and the approved Summary of Product Characteristics [ELIGARD 22.5 mg, Summary of Product Characteristics 2015].

1.3 Summary of Key Safety Information for ELIGARD®

The most commonly reported adverse reactions are hot flushes, nausea, malaise and fatigue and transient local irritation at the site of injection. Mild hot flushes occur in approximately 58% of patients.

The following very common (>1/10) AEs were reported during clinical studies with ELIGARD® in patients with advanced prostatic carcinoma: hot flushes, ecchymoses, erythema, fatigue, injection site burning, and injection site paresthesia.

Other AEs which have been reported in general to occur with leuprorelin acetate treatment include decrease in libido (pharmacological consequence of testosterone deprivation), peripheral edema, pulmonary embolism, palpitations, myalgia, muscle weakness, chills, dyspnea, peripheral vertigo, rash, amnesia, visual disturbances and skin sensation.

Local AEs reported after injection of ELIGARD® 22.5 mg are typical of those frequently associated with similar subcutaneously injected products. Mild transient burning following injection is very common. Stinging, pain and bruising are common. Generally, these localized AEs following subcutaneous injection are mild and described as being of brief duration.

Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with GnRH agonists. It can be anticipated that after long periods of treatment with leuprorelin acetate bone may show increasing signs of osteoporosis.

Treatment with leuprorelin acetate can cause exacerbations of signs and symptoms of the disease during the first few weeks. If conditions such as vertebral metastases and/or urinary obstruction or hematuria are aggravated, neurological problems such as weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms may occur. Short term anti-androgen therapy may ameliorate these symptoms.

1.4 Risk-Benefit Assessment

The expected benefits of treatment in this study are the alleviation of symptoms and improved QoL. Expected risks are associated with the AE profile of the drug. The incidence of expected AEs is summarized in **Section 1.3**. Study procedures are limited to blood sampling for determination of testosterone and PSA levels and QoL assessment.

2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

2.1 Study Objectives

The objectives of this Phase IV, prospective, interventional study are to evaluate the safety, efficacy, and QoL of ELIGARD® in hormone-dependent prostate cancer patients in Asia.

Primary Objective:

To establish the safety profile of ELIGARD® in ethnic Asian prostate cancer patients.

Secondary Objectives:

1) To describe the efficacy of ELIGARD® 22.5 mg (3-monthly formulation) in controlling PSA and testosterone levels
2) To assess HRQoL through QoL questionnaires – EORTC QLQ-PR25 and EQ5D-5L

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This is a multicenter, prospective, single-arm, interventional study to assess the safety, efficacy, and QoL of ELIGARD® 22.5 mg (3-monthly formulation) in male patients with prostate adenocarcinoma who fulfill the eligibility criteria in Asia.

This study will be conducted in approximately 20 centers in 8 countries (Hong Kong, Indonesia, Malaysia, Philippines, Singapore, Taiwan, Thailand and Vietnam). The planned total duration of this study is 30 months from the date when the first patient is enrolled until 3 months after the last dose of ELIGARD® 22.5 mg administration. The patient population includes male Asian patients diagnosed with prostate cancer who will receive ELIGARD® 22.5 mg (3-monthly formulation) depot formulation between the periods of Q2 2017 through Q3 2018. Patients for whom the treating physician has decided to initiate treatment with ELIGARD® 22.5 mg will be approached for enrollment into this study. The enrollment period will be up to 12 months. Patients will be prescreened to confirm access to ADT prior to informed consent. Following written informed consent by the patient and confirmation of eligibility, patients will be treated for 1.5 years (18 months), with ELIGARD® 22.5 mg being administered at baseline, 3rd month, 6th month, 9th month, 12th month and 15th month. AE and SAE collection will start at baseline until the follow-up visit at 18 months (*see **Section 5.6** for AE collection and SAE reporting*). QoL will be measured at baseline, 6th month, 12th month and 18th month. The PSA and testosterone levels will be assessed at all scheduled visits and during the follow-up visit. Any other assessments including imaging tests are not mandatory and will be performed according to routine standard of care and physician's discretion. Patients will be followed up at 18th month in the physician's office. The time window for each visit following baseline is +/- 14 days. At the 18th month, treatment with ELIGARD® or other alternatives as deemed appropriate by the investigator may

be continued. ELIGARD® or other alternatives will not be provided after the 15th month dose. Treatments administered after the 15th month or last visit, not limited to LHRH analogues, will be at the investigator's discretion and such data will not be collected. Patients who discontinue ELIGARD® will be followed up for monitoring of AEs for a period of 3 months, provided consent is not withdrawn. The reason for discontinuation of ELIGARD® will also be noted. Key data elements to be collected are detailed in **Section V Flow Chart and Schedule of Assessments** and in **Section 8.1.1 Data Collection**.

The sample size planned for this study is approximately 107 enrolled prostate cancer patients. The sample size was calculated based on the percentage of ELIGARD®-related AEs, as well as the desired width of its confidence interval (CI).

A Study Steering Committee was formed to refine the design, conduct, analysis and reporting of the study. It is composed of international experts specializing in the treatment of prostate cancer. Outside experts will be designated by the Steering Committee to provide specific guidance as needed throughout the study. A separate Publication Steering Committee will be formed to oversee planning of publications related to the ELIGANT study. Publication Steering Committee membership will include at a minimum a Steering Committee representative and a representative of the Sponsor.

This multinational, multi-center study shall start with obtaining written approval from the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and Regulatory Authorities. Registration with clinical trial registries in respective countries will be submitted when necessary.

2.2.2 Dose Rationale

ELIGARD® 22.5 mg (1 injection every 3 months) is the dosage that will be used in this study because it is the most widely used formulation in Asian countries and is available in all the Asian countries participating in this study.

ELIGARD® 22.5mg is administered subcutaneously and provides continuous release of leuprolide acetate over a 3-month treatment period. ELIGARD® is a long-acting depot formulation that uses Atrigel® delivery system (a biodegradable polymer matrix) to deliver leuprolide acetate at a controlled rate over a therapeutic period.

Subcutaneous administration of ELIGARD® is as per the label and approved indications of ELIGARD®. (*Refer to the current local ELIGARD prescribing information.*)

2.3 Endpoints

2.3.1 Primary Endpoints

ELIGARD®-related AEs throughout the entire observation period, as determined by the opinion of the investigator

2.3.2 Secondary Endpoints

- Efficacy outcomes of clinical response based on testosterone and PSA levels (Testosterone level and PSA will be assessed for all patients at each scheduled visit, prior to administering ELIGARD®, and at the follow-up visit.)
- HRQoL assessment through QoL questionnaires – EORTC QLQ-PR25 (prostate cancer disease specific PRO) and EQ5D-5L (generic PRO) measured at 0, 6, 12, and 18 months.

2.3.3 Exploratory Endpoints

Not applicable.

3 STUDY POPULATION

3.1 Selection of Study Population

This study is designed for male patients with:

- Locally advanced prostate cancer with biochemical relapse following radical prostatectomy and/or radiotherapy (see inclusion criteria 4)
- Hormonal treatment-naive advanced or metastatic prostate cancer.

Centers that decide to initiate treatment of prostate cancer patients with ELIGARD® will be identified and requested to approach patients for consent to participate. In each site, a planned number of enrolled patients will be established according to the capability of the site. Should the investigator wish to include more patients than initially planned, the approval of the sponsor must be obtained.

In order to reduce patient selection bias, each patient who is expected to receive ELIGARD® treatment and consent to participate must be assessed at the baseline visit. Eligible patients who fulfill all inclusion criteria and none of the exclusion criteria will be enrolled consecutively into the study at each site. In case a patient is not eligible, the reason for non-eligibility must be documented in the patient log file.

Enrollment will be competitive and will be stopped when the anticipated number of patients has been achieved across all study sites.

3.2 Inclusion Criteria

A patient for whom the physician has decided to initiate treatment with LHRH agonist 3 monthly formulation in standard clinical practice will be approached for enrolment into this study.

1. Ethnic Asian male patient above 18 years of age
2. Willing and able to provide written informed consent
3. Biopsy-proven prostate adenocarcinoma
4. Locally advanced prostate cancer with biochemical relapse following radical prostatectomy and/or radiotherapy. Biochemical relapse [Mottet et al, 2006] is defined as:
    - PSA > 2 ng/ML following radiotherapy, or
    - Two consecutive PSA values > 0.2 ng/mL and rising above the nadir following radical prostatectomy

    OR

Hormonal treatment-naive advanced or metastatic prostate cancer patient who has not received chemotherapy and has no plans to undergo treatment with chemotherapy at study entry

5. Patient who indicates that once the study is completed, he expects having access to ADT, either medical or surgical, within the local healthcare system (either through public/ private health insurance or out of pocket payment).

3.3 Exclusion Criteria

1. Patient with castrate resistant prostate cancer (CRPC)
2. Patient who previously underwent bilateral orchiectomy
3. Patient who has received prior treatment with LHRH analogues
4. Prior or concomitant treatment with systemic chemotherapy. A patient where there is a likelihood to receive systemic chemotherapy should not be enrolled
5. Life expectancy of < 1 year due to comorbidities
6. Participation in another interventional clinical trial within 1 month prior to study entry or during the duration of the study
7. Physician is planning to give the patient intermittent ADT at the time of study entry
8. Patient receiving non-palliative radiotherapy within 3 months prior to study entry
9. Patient receiving adjuvant ADT in combination with definitive radiotherapy
10. Patient with metastatic hormonal treatment-naive prostate cancer, for whom chemo-hormonal treatment (combination of Docetaxel and ADT) is indicated.
11. Patient with hypersensitivity to GnRH, GnRH agonist analogs or any of the components of ELIGARD®
12. Patient with any contraindication for ELIGARD® use based on local prescribing information

While patients enrolled or expected to be enrolled in clinical trials of investigational therapy are not allowed, their participation in this interventional study will not preclude them from future participation in other non-interventional studies.

Waivers to the exclusion criteria will NOT be allowed.

4 TREATMENTS

4.1 Identification of Investigational Product

4.1.1 Test Drug(s)

ELIGARD® 22.5 mg is intended to be administered subcutaneously and provides continuous release of leuprolide acetate over a 3-month treatment period. ELIGARD® is a long-acting depot formulation that uses Atrigel® delivery system (a biodegradable polymer matrix) to deliver leuprolide acetate at a controlled rate over a therapeutic period.

Subcutaneous administration of ELIGARD® is as per the label and approved indications of ELIGARD®. *(Refer to the current local ELIGARD prescribing information.)*

ELIGARD® will be prescribed by treating physician according to local prescribing information. ELIGARD® will be provided in this study. ELIGARD® should be stored in a refrigerator (2-8°C), and will be stable for 24 months from the date of manufacturing when stored at 2-8°C.

4.1.2 Comparative Drug(s)

Not applicable as this is a single arm interventional study on ELIGARD®.

4.1.3 Drug(s) for Screening

Not applicable.

4.1.4 Rescue Drug(s)

Not applicable.

4.2 Packaging and Labeling

ELIGARD® used in this study will be prepared, packed and labelled under the responsibility of the qualified staff at Astellas Pharma Singapore or Sponsor's designee in accordance with Astellas Pharma Singapore or Sponsor's designee standard operating procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International Conference on Harmonisation – Good Clinical Practice (ICH GCP) guidelines, and applicable local laws/regulations. The packaging and labeling of the study medication will be outsourced to a preferred contractor.

ELIGARD® 22.5 mg will be repackaged into another carton box. A label identifying the contents as an investigational drug and other required information will be applied to the outer carton box. A medication number will identify the ELIGARD® packages and will be captured in the electronic case report form (eCRF). This number will be used for the allocation of the medication at a particular visit to a certain patient.

4.3 Study Drug Handling

Current ICH GCP guidelines require the investigator to ensure that study drug deliveries from the Sponsor are received by the investigator/or designee and

- that such deliveries are recorded,
- that the study drug is handled and stored according to labeled storage conditions,
- that the study drug has appropriate expiry/retest and is only dispensed to study patients in accordance with the protocol, and
- that any unused study drug is returned to the Sponsor.

Drug inventory and accountability records for the study drug will be kept by the investigator/or designee. Study drug accountability throughout the study must be documented and reconciled. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drugs to any persons except the eligible patients in this study in accordance with the protocol.
- The investigator or designee will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these test drugs.
- A study drug inventory will be maintained by the investigator or designee. The inventory will include details of material received and a clear record of when they were dispensed and to which patient.
- At the conclusion or termination of this study, the investigator or designee agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and/or returned medication. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.
- The site must return unused study drug to the Sponsor or designee at the end of the study or upon expiration.

4.4 Blinding

Not applicable as this is an open label study on ELIGARD®.

4.5 Assignment and Allocation

Not applicable as this is a single-arm interventional study on ELIGARD®.

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drug(s) and Other Medication(s)

5.1.1 Dose/Dose Regimen and Administration Period

ELIGARD® 22.5mg is administered subcutaneously and provides continuous release of leuprolide acetate over a 3-month treatment duration. ELIGARD® is a long-acting depot formulation that uses Atrigel® delivery system (a biodegradable polymer matrix) to deliver leuprolide acetate at a controlled rate over a therapeutic period.

Subcutaneous administration of ELIGARD® 22.5mg is as per the label and approved indications of ELIGARD®. Refer to the current local ELIGARD® prescribing information.

ELIGARD® will be prescribed by treating physician according to local prescribing information. ELIGARD® will be provided by the sponsor during the conduct of this study.

5.1.2 Increase or Reduction in Dose of the Study Drug(s)

Only ELIGARD® 22.5mg will be used for this study, thus, dose changes are not allowed.

5.1.3 Previous and Concomitant Treatment

Bicalutamide 50 mg O.D. or a similar anti-androgen is an allowed concomitant medication for flare prevention only. Additional administration of an appropriate anti-androgen should be considered beginning at least 3 days to 4 weeks prior to the first ELIGARD® injection and continuing for the first 2 to 3 weeks of treatment to avoid any flare reaction. Use of bicalutamide or similar anti-androgen beyond 3 weeks after starting ELIGARD therapy and for reasons other than flare prevention is not allowed.

Note: Anti-androgens will not be provided by the Sponsor. Patients will be responsible for any costs associated with anti-androgen therapy.

5.1.4 Treatment Compliance

Study patients should be counseled on the need to meet 100% compliance with the study drug. The investigator or designee should ensure that study patients meet this goal throughout the study period. Since the study drug will be administered by qualified study personnel at the research site during each study visit, compliance will be verified by checking that the study drug was correctly administered during each patient's scheduled visit. Compliance of the study drug will be monitored and documented. If compliance is 80%, the investigator or designee is to counsel the patient and ensure steps are taken to improve compliance and adherence to the study schedule. Patients who are less than 80% compliant with the dosage regimen for any 2 consecutive visit periods (window ± 14 days) during the study should be withdrawn.

5.1.5 Criteria for Continuation of Treatment

A patient can continue in this study until the Month 18, provided none of the discontinuation criteria (see Section 6.1) are met.

5.1.6 Restrictions During the Study

The following drugs are prohibited to be used throughout the study *(see Section 12.2)*:

1. Other LHRH analogues,
2. LHRH antagonists and other agents (approved or investigational) which are known to impact on testosterone or PSA level,
3. Ketoconazole,
4. Estrogens,
5. Herbal medications that may affect PSA levels (i.e., saw palmetto),
6. Androgens (testosterone, dihydroepiandrosterone, etc.),
7. Abiraterone,
8. Enzalutamide,
9. Chemotherapy agents including docetaxel and platinum drugs

5.2 Assessment at Prescreening Visit

The physicians will review the inclusion/exclusion criteria of patients to assess patients' eligibility for ELIGARD® 22.5 mg 3-month depot at prescreening visit. The assessment of patient's access to medical or surgical ADT after the trial ends will be based on the interview by the physician at prescreening visit.

5.3 Demographics and Baseline Characteristics

5.3.1 Informed Consent and Inclusion/Exclusion Criteria

The informed consent must be obtained at baseline visit. The investigator will also review the inclusion/exclusion criteria for each patient at baseline visit.

5.3.2 Demographics

Demographic information will be collected at the baseline visit and will include date of birth (or age, if local regulations do not allow recording of patient's date of birth), race as described by the patient (unless local regulations do not allow recording of patient's race), and highest education level.

5.3.3 Medical History

Medical history will be collected at the baseline visit and will include diabetes, hypertension, cardiac disorders and any significant conditions or diseases other than prostate cancer that occurred prior to informed consent.

5.3.4 Family History for Prostate Cancer

A complete family history of the prostate cancer will be collected at the baseline visit. This includes documenting the patient's family history of brother(s), father, first-degree relative(s) and/or second-degree relative(s) with prostate cancer, including the age at the time of diagnosis.

5.3.5 Diagnosis of the Target Disease, Severity, and Duration of Disease

Baseline disease characteristics for prostate cancer will be collected at baseline visit, including time since diagnosis, Gleason score at initial diagnosis, Tumor, Nodes, Metastasis (TNM) classification, staging, surgical history, biopsy results, dates and types of anti-neoplastic therapy including radiation therapy prior to study inclusion (including number of cycles, treatment duration, time interval since previous treatments), Eastern Cooperative Oncology Group (ECOG) status, bone lesions, soft tissue disease, visceral disease, and pain (using the Visual Analogue Scale [VAS] 0-10).

5.3.6 Most Important Factors for Selection of Treatment

The reasons for selection of treatment with ELIGARD® 22.5 mg will be collected at the baseline visit. The most important factors will be determined by physicians and recorded.

5.4 Efficacy Assessment

Efficacy outcomes of clinical response based on testosterone and PSA levels, both of which will be tested for all patients at each scheduled visit, prior to administering ELIGARD®, and at the follow up visit.

HRQoL will be assessed through EORTC QLQ-PR25 and EQ5D-5L. EORTC QLQ-PR25 is a prostate cancer module for the assessment of HRQoL. EORTC QLQ-PR25 is designed for self-completion by respondents. It assesses urinary symptoms, bowel symptoms, treatment-related symptoms, and sexual activity and functioning. EQ5D-5L is a standardized instrument for use as a measure of health outcome. It provides a simple descriptive profile and a single index value for health status. EQ5D-5L is designed for self-completion by respondents. It consists of 2 pages comprising the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels and the patient is asked to indicate his health state by ticking the box with the most appropriate statement.

Patients will be asked to complete an EORTC QLQ-PR25 and EQ5D-5L questionnaire at the baseline visit, 6 months, 12 months and 18 months.

5.5 Safety Assessment

5.5.1 Vital Signs

Vital information will be collected at the baseline visit and every following visit. The vital status information includes blood pressure, pulse rate, respiratory rate and weight. Height will be collected at baseline visit only.

5.5.2 Adverse Events

See **Section 5.6 Adverse Events and Other Safety Aspects** for information regarding AE collection and data handling.

5.5.2.1 Adverse Events of Possible Hepatic Origin

See **Appendix 12.3 Liver Safety Monitoring and Assessment** for detailed information on liver abnormalities, monitoring and assessment, if the AE for a patient enrolled in a study and receiving study drug is accompanied by increases in liver function testing (LFT, e.g., aspartate transaminase [AST], alanine aminotransferase [ALT], total bilirubin [TBL], etc.) or is suspected to be due to hepatic dysfunction.

5.5.2.2 Treatment for AEs and SAEs

Information pertaining to the treatment for AEs and SAEs will be collected at each visit, if applicable. The information will include any intervention (e.g. medication(s), procedure(s), radiography, surgical treatment, visits to Accident & Emergency department and/or ambulatory clinic, hospitalization) to treat AEs and SAEs. The duration of treatment and hospitalization will also be collected.

5.5.3 Laboratory Assessments

Testosterone and PSA levels will be assessed for all patients at each scheduled visit, prior to administering ELIGARD®, and at the follow up visit. Information on other laboratory tests will only be collected if the tests are done within routine clinical practice. The laboratory tests include lactate dehydrogenase (LDH), alkaline phosphatase (ALP), hematology, LFT and RFT.

5.5.4 Imaging

Data on tumor evaluation/ radiographic assessments will only be collected if available. Radiographic evaluation includes computerized tomography (CT) scan, positron emission tomography (PET) scan, magnetic resonance imaging (MRI), Bone scan, X-ray, ultrasound or any other imaging test which have been performed as part of standard of care.

5.6 Adverse Events and Other Safety Aspects

AE and SAE collection will start from signing of informed consent form (ICF) until the follow-up visit at 18 months, or early withdrawal/discontinuation.

5.6.1 Definition of Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a patient administered a study drug or has undergone study procedures and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, electrocardiogram [ECG] data, physical exam) should be defined as an AE only if the abnormality meets 1 of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

5.6.2 Definition of Serious Adverse Events (SAEs)

An adverse event will be considered to be "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Results in death
- Is life threatening (an AE is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above. These events,

including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Safety events of interest on the medicinal products administered to the patient as part of the study (e.g., study drug, comparator, and background therapy) that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of the medicinal product(s)
- Suspected abuse/misuse of the medicinal product(s)
- Inadvertent or accidental exposure to the medicinal product(s)
- Medication error involving the medicinal product(s) (with or without subject/patient exposure to the Sponsor medicinal product, e.g., name confusion)

All of the events of interest noted above should be recorded on the eCRF. Any situation involving these events of interest that also meets the criteria for an SAE should be recorded on the AE page of the eCRF and marked 'serious' and on SAE worksheet. Refer to **Section 5.6.5** below for SAE reporting timeline and procedure.

The Sponsor has a list of events that they classify as "always serious" events (refer to the Appendix). If an AE is reported that is considered to be an event per this classification as "always serious", additional information on the event may be requested.

5.6.3 Criteria for Causal Relationship to the Study Drug

AEs that fall under either "Possible" or "Probable" should be defined as "AEs whose relationship to the study drugs could not be ruled out";

Causal relationship to the study drug	Criteria for causal relationship
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re-administration (rechallenge) or withdrawal (dechallenge).

For this study, an ELIGARD® -related AE is defined as an adverse event in a patient administered ELIGARD® where a causal relationship is at least a reasonable possibility (drug event with either a possible or probable causal relationship), as determined by the investigator. Adverse events listed in the local label should be used by the investigator as reference safety information to understand whether an adverse event is expected with the use of ELIGARD®. This understanding should inform their causality assessments.

5.6.4 Criteria for Defining the Severity of an Adverse Event

AEs, including abnormal clinical laboratory values, will be graded using the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Event (CTCAE) guidelines (Version 4.03). The items that are not stipulated in the NCI-CTCAE Version 4.03 will be assessed according to the criteria below and entered into the eCRF:

Grade	Assessment Standard
1-Mild	Asymptomatic, or mild symptoms, clinical or diagnostic observations noted; intervention not indicated.
2-Moderate	Local or noninvasive intervention indicated.
3-Severe	Medically significant but not immediately life threatening, hospitalization or prolonged hospitalization.
4-Life Threatening	Life threatening consequences, urgent intervention indicated
5-Death	Death related to AE

5.6.5 Reporting of Serious Adverse Events (SAEs)

In the case of an SAE, the investigator should complete and submit an SAE Worksheet in the eCRF containing all information that is required by the Regulatory Authorities to the Sponsor/contract research organization (CRO) within 24 hours of awareness following the procedure outlined in the Safety Reporting Guide provided to the sites. AEs should be reviewed

by Investigator in a timely fashion, i.e., if an AE is upgraded to an SAE, these need to be reported to the Sponsor /delegated designee within 24 hours. If completion of the SAE worksheet is not possible through the eCRF, email or by fax within 24 hours, the Sponsor's local drug safety contact/ CRO should be informed by phone.

For contact details, see **Section II Contact Details of Key Sponsor's Personnel**.

If there are any questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Monitor or his/her designee (see **Section II Contact Details of Key Sponsor's Personnel**).

Follow-up information for the event should be sent promptly (within 7 days of the initial notification).

Full details of the SAE should be recorded on the medical records and on the eCRF.

The following minimum information is required:

- ISN/Study number,
- Patient number, sex and age,
- The date of report,
- A description of the SAE (event, seriousness of the event), and
- Causal relationship to the study drug.

The Sponsor or Sponsor's designee will submit expedited safety reports to the regulatory agencies in accordance to the local regulations, and will inform the investigators of such regulatory reports. Investigators must submit safety reports as required by their IRB/IEC within timelines set by regional regulations. Documentation of the submission to and receipt by the IRB/IEC of expedited safety reports should be retained by the site. The investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor.

Investigators may contact the Sponsor's Medical Monitor for any other problem related to the safety, welfare, or rights of the patient.

Reporting of SAEs in case of ELIGARD® treatment discontinuation

For patients who discontinue ELIGARD® treatment, AE monitoring should be continued for a period of 3 months from the date of last administration of ELIGARD®, provided consent is not withdrawn. AE documentation and SAEs reporting should be continued during this period of time. SAEs that are considered to be related to ELIGARD® occurring after the end of the observation period or after end of the follow-up period should be reported according to local law/guidelines within the spontaneous reporting system.

Safety Observations

The investigator should take all appropriate measures to ensure the safety of the patients. The outcome of all reported SAEs (e.g., resolution, death) will be followed up and documented. Reporting to the relevant Regulatory Authorities according to national regulations will be done by the Sponsor.

5.6.6 Follow-up of Adverse Events

All AEs occurring during or after the patient has discontinued the study are to be followed-up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized.

If during AE follow-up, the AE progresses to an "SAE", or if a patient experiences a new SAE, the investigator must immediately report the information to the Sponsor.

Please refer to **Appendix 12.3 Liver Safety Monitoring and Assessment** for detailed instructions on Drug Induced Liver Injury (DILI).

5.6.7 Monitoring of Common Serious Adverse Events

Common SAEs are SAEs commonly anticipated to occur in the study population independent of drug exposure. SAEs classified as "common" are provided in **Appendix 12.4 Common Serious Adverse Events** for your reference. The list does NOT change your reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed above. The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common serious adverse events" as specified in **Appendix 12.4 Common Serious Adverse Events**. The Sponsor will monitor these events throughout the course of the study for any change in frequency. Any changes to this list will be communicated to the participating investigational sites. Investigators must report individual occurrences of these events as stated in **Section 5.6.5 Reporting of Serious Adverse Events.**

5.6.8 Procedure in Case of Pregnancy of Partner

This study involves male prostate cancer patient. If a partner of a male patient becomes pregnant during the study while taking the medication the investigator should report the information to the Sponsor/delegated designee within 24 hours of awareness as if it is an SAE. The expected date of delivery or expected date of the end of the pregnancy of partner, paternal drug exposure etc., should be included in this information. If limited data are reported, reasonable effort should be made to complete these.

The investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE and will report the outcome to the Sponsor.

When the outcome of the pregnancy falls under the criteria for SAEs (spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly [including anomaly in a miscarried fetus]), the investigator should respond in accordance with the report procedure for SAEs. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below.

- "Spontaneous abortion" includes miscarriage, abortion and missed abortion
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug
- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as "possible" by the investigator
- In the case of a delivery of a living newborn, the "normality" of the infant is evaluated at the birth
- Unless a congenital anomaly are identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination

5.6.9 Emergency Procedures and Management of Overdose

In the event of suspected overdose, refer to the approved Package Insert or local product information supplied by Astellas.

5.6.10 Supply of New Information Affecting the Conduct of the Study

When new information becomes available necessary for conducting the clinical study properly, the Sponsor will inform all investigators involved in the clinical study as well as the regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

5.7 Test Drug Concentration

Not applicable.

5.8 Other Measurements, Assessments or Methods

5.8.1 Prostate Cancer Status

Information on prostate cancer status will be collected at the baseline visit and each follow-up visit. The information will include stage of prostate cancer, bone metastasis, soft tissue disease, visceral disease, pain (using VAS 0-10), and ECOG status.

5.8.2 Supportive Care

Information on other supportive care treatment will be collected at the baseline visit and each follow-up visit, and will be recorded in the eCRF. The information will include type of

treatment, drug dose, schedule and duration, supportive care measures, other concomitant medications related to cancer (e.g., pain medications, bone protective medications, spinal cord decompression surgery, palliative radiotherapy)

5.8.3 Concomitant Medications Assessment

Information on concomitant medication will be collected at the baseline visit and each follow-up visit, and will be recorded in the eCRF. The information will include generic or brand names of the medication, the dose, unit, route, frequency, start and end dates and the reason for taking the medication.

5.9 Total Amount of Blood

The total volume of blood to be drawn is 35 ml during the entire study (from baseline to follow-up visit) with 5 ml per visit.

6 DISCONTINUATION

6.1 Discontinuation of Individual Patients

A discontinuation is a patient who enrolled in the study and for whom study treatment is permanently discontinued prematurely for any reason.

A patient is free to withdraw from the study for any reason, at any time, without reason for doing so and without penalty or prejudice.

A patient will be discontinued from the study in the case of:

1. Withdrawal of consent - patient decision to withdraw from further participation in the study
2. Patient safety is at risk (at the discretion of the treating physician)
3. Patient develops CRPC as determined by European Association of Urology (EAU) Prostate Cancer Guidelines 2016
4. Patient is lost to follow-up
5. Patient death during the study
6. Patent misses consecutive visit periods (window ± 14 days) during the study
7. Patient who is less than 80% compliant with the dosage regimen for any 2 consecutive visit periods (window ± 14 days) during the study.
8. Site terminated by the Sponsor
9. Study terminated by the Sponsor
10. Cessation of treatment with ELIGARD® (at the discretion of the treating physician). The reasons for stopping treatment will be noted (e.g., PSA progression, radiographic progression, clinical progression, AE, drug administration issues, other).
11. Patient takes prohibited medications as described in Section 5.1.6 and Section 12.2

For patients that discontinue from the study, the reason for discontinuation should be recorded in the eCRF. Patients that discontinue will have an Early Withdrawal visit 3 months after the last administration of ELIGARD® for safety assessment. At the end of a patient's involvement in this study, the Investigator must ensure that all outstanding data entry is entered in the eCRF unless the patient withdrew consent for their data to be used.

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the Sponsor/delegated designee.

6.3 Discontinuation of the Study

The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

7 STATISTICAL METHODOLOGY

Data analysis will be performed by the designated CRO in accordance with the CRO's SOPs for statistics and clinical programming with oversight from MA Statistics of the Sponsor. All study specific processes and definitions will be documented. Data analysis will be performed in adherence to Astellas data standards.

Analyses that will be performed on the primary and secondary variables are described in this section. A more technical and detailed elaboration of the statistical analysis of the primary and secondary variables and other data will be included in a separate Statistical Analysis Plan (SAP) and result tables specification manual. The SAP will be finalized before the database soft lock at the latest. Any changes from the analyses planned in SAP will be justified in the Clinical Study Report.

Summary statistics of all variables (demographic and clinical) will be produced in the form of tables. Descriptive statistics (mean, median, standard deviation [SD], etc.) in addition to graphical representation of the data (plots, histograms, etc.) will be presented. For continuous variables, descriptive statistics will include the number of patients (n), mean (for observed values and absolute changes from baseline), SD, median, minimum and maximum. Two-sided 95% CI will be calculated for mean changes from baseline. For categorical variables, the number and percentage of patients by each category will be tabulated by visit. The number of missing values will be specified for each variable. Cross tabulations will be produced to explore relationships between variables. No formal statistical comparisons will be performed.

7.1 Sample Size

This study targets to enroll approximately 107 prostate cancer patients.

The sample size was calculated based on the estimated percentage of ELIGARD®-related AEs, as well as the desired width of its 95% CI. Prior clinical studies on ELIGARD® have shown an ELIGARD®-related AEs rate of around 50% of patients during a six-month treatment period [ELIGARD Investigator's Brochure, June 2008; Tombal & Berges, 2007]. With the assumption that the percentage of ELIGARD®-related AEs will be 50%,a sample size of 96 completed patients is sufficient for estimating a Wald 95% CI with a width of 20% (+/- 10% from the middle), based on a finite population correction, with factor N=10,000.

Therefore, the total sample size of this study, assuming a drop-out rate of 10%, is 107 patients.

PASS 14 Power Analysis and Sample Size Software (2015) version number 14.0.2 was used in the sample size calculation (NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass).

7.2 Analysis Set

Detailed criteria for analysis sets will be laid out in Classification Specifications and the allocation of patients to analysis sets will be determined prior to database hard-lock.

7.2.1 Full Analysis Set (FAS)

The full analysis set (FAS) will consist of all patients who are enrolled and receive at least 1 dose of study drug and have at least 1 post baseline measurement of PSA and testosterone levels. This will be the primary analysis set for efficacy analyses.

7.2.2 Per Protocol Set (PPS)

The per protocol set (PPS) will consist of the subset of the FAS who do not meet criteria for PPS exclusion. These criteria are to capture relevant non-adherence to the protocol and are listed below:

- Entered into the study even though they did not satisfy entry criteria
- Developed withdrawal criteria during the study and was not withdrawn (Patients who discontinued the study for efficacy-related reasons, such as insufficient therapeutic effect, will be included in the PPS.)
- Full dose was not administered or drug reconstitution was not performed as prescribed
- Patients with treatment compliance <80%
- Patients who used prohibited concomitant medication as defined in protocol

Further criteria may be defined in the SAP. The PPS will be a secondary analysis set for efficacy analyses. Select demographic and baseline characteristics may also be summarized for the PPS.

7.2.3 Safety Analysis Set (SAF)

For the statistical summary of the safety data, the safety analysis set (SAF) will be used. The SAF consists of all patients from whom at least 1 ELIGARD® injection is received and any follow-up safety information is available.

7.2.4 Pharmacokinetic Analysis Set (PKAS)

Not applicable.

7.2.5 Pharmacodynamic Analysis Set (PDAS)

Not applicable.

7.3 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized for the SAF and PPS. Descriptive statistics will include number of patients, mean, SD, minimum, median and maximum for continuous endpoints, and frequency and percentage for categorical endpoints.

7.4 Analysis of Efficacy

Efficacy analysis will be conducted on the FAS and PPS. The interpretation of results from statistical tests will be based on the FAS. The PPS will be used to assess the robustness of the results from the statistical tests based on the FAS.

7.4.1 Analysis of Primary Endpoint

Not applicable as the primary analysis of this study is a safety analysis.

7.4.2 Analysis of Secondary Endpoints

Descriptive statistics will be presented for the following:

- Percentage of patients with Testosterone <20, 20-50 and >50 ng/dL at 1 year and at 1.5 years
- Time to PSA progression: calculated from date of first administration of ELIGARD® 22.5 mg to PSA progression
- PSA progression will be defined as a 25% or greater increase and an absolute increase of 2 ng/mL or more from the nadir is documented, which is
    - Confirmed by a second value obtained 3 or more weeks later
    - If not done based on standard clinical practice, the confirmatory PSA measurement should be performed at the next routine study visit.

      Note: The aim is to detect time to PSA progression and not to assess whether the patient has progressed to CRPC. Imaging and other modalities should be used to determine if the patient has moved to CRPC, which is outside the scope of this study
- HRQoL: (EORTC QLQ-PR25 and EQ-5D-5L) at baseline and following scheduled visits as well as change from baseline

7.4.3 Analysis of Exploratory Endpoints

Not applicable as there are no exploratory objectives in this study.

7.5 Analysis of Safety

7.5.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of AEs, SAEs, Severe AEs (defined as AEs graded $\geq$ 3 according to NCI-CTCAE guidelines Version 4.03), AEs leading to treatment discontinuation, and ELIGARD®-related AEs will be summarized by System Organ Class (SOC), Preferred Term (PT). The number and percentage of AEs by severity will also be summarized. AEs that occur after

receiving CRPC management will be presented separately. All AEs, including information described in following subsections, will be listed.

7.5.1.1 Incidence of ELIGARD® Related Adverse Events

ELIGARD®-related AEs are AEs that are reported to be related to ELIGARD® (possible or probable) as determined by the investigator.

All ELIGARD®-related AEs will be summarized according to their severity, NCI CTCAE Grade, outcome, course of event, seriousness, action taken with ELIGARD® and treatment required to manage the AE for SAF set.

To analyze the incidence of ELIGARD®-related AEs and SAEs during the observation period, 2-sided 95% symmetric CIs of incidence rates based on normal approximation will be presented after adjusted for a finite sample size of 10000. All SAF subjects will be counted, and separate summaries shall be performed for ELIGARD® -related AEs and SAEs.

Time to first occurrence of ELIGARD® -related AEs and SAEs will be presented using Kaplan-Meier (KM) plots. If applicable, estimated median time to first event together with a 95% CI will be prepared. In addition, KM estimates of incidence rates of ELIGARD® -related AEs and SAEs will be summarized at each scheduled visit time-point, together with a 95% CI.

Of note, summaries of ELIGARD®-related AEs and SAEs that occurred after receiving CRPC management will be presented separately.

Details of statistical analyses for primary safety endpoint will be described in the statistical analysis plan.

7.5.1.2 Treatment for ELIGARD® Related Adverse Events

Interventions taken to manage ELIGARD® -related AEs, including medications, procedures, radiography, and hospitalization together with visits to Accident & Emergency Department and/or ambulatory clinic, will be summarized by their categories and coded terms whenever applicable. In addition, occurrence count and cumulative duration of each intervention and hospitalization record for each subject will be summarized and presented for SAF.

7.5.2 Laboratory Assessments

For quantitative laboratory measurements descriptive statistics will be used to summarize results and change from baseline by time point. Shifts relative to normal ranges from baseline to each time point during treatment period in lab tests will also be tabulated. Laboratory data will be displayed in listings. Laboratory data will include LDH, ALP, Hematology, LFT and RFT, etc.

7.5.3 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline by time. Vital signs data will be displayed in listings.

7.5.4 Imaging

Descriptive statistics will be used to summarize imaging data if available.

7.6 Protocol Deviations and Other Analyses

Protocol deviations as defined in **Section 8.1.6 Protocol Deviations** (PD) will be summarized for all patients. A data listing will be provided by site and patient.

The protocol deviation criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Full dose was not administered or drug reconstitution was not performed as prescribed,

PD4 - Received excluded concomitant treatment.

7.7 Interim Analysis

A minimum of 1 interim analysis will be conducted when 50 patients complete 1 year of follow-up. As there are no statistical hypothesis tests in the planned analysis, the conduct of interim analyses will not have any statistical implications on the final study outcome.

7.8 Handling of Missing Data, Outliers, Visit Windows, and Other Information

The amount and potential effect of missing data will be explored and detailed further in the SAP. In general, missing data will not be imputed and the data will be analyzed as they are recorded in the study case report forms (CRFs). However, if more than 10% of data is missing for 1 or more key variables, the impact of missing data on the analysis will be discussed, and the pattern of missing data will be explored. If there is evidence of bias in the missing data, and variables that are considered good predictors of the missing data are available, the multiple imputation method at the study level may be used to replace missing values as secondary exploratory analyses. If the multiple imputation method is used, a sensitivity analysis will be carried out comparing results from the complete case analysis (where records with missing data will be dropped) and the full set analysis (with imputed data).

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The investigator or site designee will enter data collected using an Electronic Data Capture (EDC) system. In the interest of collecting data in the most efficient manner, the investigator or site designee should record data (including laboratory values, if applicable) in the eCRF.

The investigator or site designee is responsible for ensuring that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site.

The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

Laboratory tests are performed at each site's local laboratory. Laboratory data will be transferred electronically to the Sponsor or designee at predefined intervals during the study. The laboratory will provide the Sponsor or designee with a complete and clean copy of the data.

Paper Patient Reported Outcome (pPRO):

EORTC QLQ-PR25 and EQ-5D-5L will be completed by the patient on paper. The investigator or site designee should review questionnaire data while the patient is at the site. The investigator or site designee will enter the questionnaire data directly into the EDC system. The paper questionnaires will be kept at sites.

8.1.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study patients and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the patient.

The following information should be included in the source medical records:

- Demographic data (age, sex, race, ethnicity, height and body weight)
- Inclusion and exclusion criteria details
- Participation in study and original signed and dated ICFs
- Visit dates
- Medical history and physical examination details (physical examination is optional)
- Key efficacy and safety data, if applicable (as specified in the protocol)
- AEs and concomitant medication

- Results of relevant examinations (e.g., X-ray films, CT scan, MRI, etc.)
- PSA and testosterone levels
- Other laboratory printouts (if applicable)
- Drug administration data
- Reason for premature discontinuation (if applicable)
- QoL questionnaires

8.1.3 Clinical Study Monitoring

The Sponsor or delegated designee is responsible for monitoring the clinical study to ensure that patient's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and ICH GCP, and study data reported by the investigator/sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The Sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.4 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the Sponsor or delegated designee as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents (refer to **Section 8.1.2**) when they are requested by the Sponsor monitors and auditors, the IRB/IEC, or regulatory authorities. The confidentiality of the patient's identities shall be well protected consistent with local and national regulations when the source documents are patient to direct access.

8.1.5 Data Management

Data Management will be coordinated by the Sponsor's designee in accordance with the delegated designee's SOPs for data management. All clinical study-specific processes and definitions will be documented by Data Management. Coding of medical terms and medications will be performed using MedDRA and World Health Organization (WHO) Drug Dictionary respectively.

The Clinical Data Interchange Standards Consortium (CDISC) datasets should be developed according to Astellas Data standards (Study Data Tabulation Model [SDTM] and Analysis Data Model [ADaM]).

8.1.6 Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of patients. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to trial patients.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

For the purposes of this protocol, deviations requiring notification to Sponsor are defined as any patient who:

- Entered into the study even though they did not satisfy entry criteria.
- Developed withdrawal criteria during the study and not withdrawn.
- Received incorrect dose.
- Full dose was not administered or drug reconstitution was not performed as prescribed.
- Received any excluded concomitant medication (***see Sections 5.1.6 and 12.2***)

When a deviation from the protocol is identified for an individual patient, the investigator or designee must ensure the Sponsor is notified. The Sponsor will follow-up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and /or efficacy of the patient to determine patient continuation in the study.

If a deviation impacts the safety of a patient, the investigator must contact the Sponsor immediately.

The investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the Sponsor and maintained within the Trial Master File (TMF).

Note: Other deviations outside of the categories defined above that are required to be reported by the IRB/IEC in accordance with local requirements will be reported, as applicable.

8.1.7 End of Trial in All Participating Countries

The end of trial in all participating countries is defined as the Last Patient's Last Visit.

8.2 Ethics and Protection of Patient Confidentiality

8.2.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) / Competent Authorities

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of patient information related to the study (e.g., advertisements used to recruit patients) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and patient information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any substantial amendments to the protocol will require IEC/IRB approval prior to implementation of the changes made to the study design at the site. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any SAEs that meet reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to patients. Written documentation of the submission to the IEC/IRB should also be provided to Sponsor.

If required by local regulations, the investigator shall make accurate and adequate written progress reports to the IEC/IRB at appropriate intervals, not exceeding 1 year.

8.2.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

8.2.3 Informed Consent of Patients

8.2.3.1 Patient Information and Consent

The investigator or his/her representative will explain the nature of the study to the patient or his/her guardian or legal representative, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the patient, the informed consent statement will be reviewed, signed and dated by the patient or his/her guardian or legal representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed ICF will be given to the patient and the original will be placed in the patient's medical record. An entry must also be made in the

patient's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the patient received a signed copy.

The signed ICFs will be retained by the investigator and made available (for review only) to the study monitor and auditor regulatory authorities and other applicable individuals upon request.

8.2.3.2 Supply of New and Important Information Influencing the Patient's Consent and Revision of the Written Information

The investigator or his/her representative will immediately inform the patient orally whenever new information becomes available that may be relevant to the patient's consent or may influence the patient's willingness to continue to participate in the study (e.g., report of ELIGARD®-related SAEs). The communication must be documented in the patient's medical records and must document whether the patient is willing to remain in the study or not.

The investigator must update their ICF and submit it for approval to the IRB/IEC. The investigator or his/her representative must obtain written informed consent from the patient on all updated ICFs throughout their participation in the study. The investigator or his/her designee must re-consent patients with the updated ICF even if relevant information was provided orally. The investigator or his/her representative who obtained the written informed consent and the patient should sign and date the ICF. A copy of the signed ICF will be given to the patient and the original will be placed in the patient's medical record. An entry must be made in the patient's records documenting the re-consent process.

8.2.4 Patient Confidentiality

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the patient to the patient's physician or to other appropriate medical personnel responsible for the patient's well-being.

The Sponsor shall not disclose any confidential information on patients obtained during the performance of their duties in the clinical study without justifiable reasons.

The Sponsor affirms the patient's right to protection against invasion of privacy. Only a patient identification number and/or initials will identify patient data retrieved by the Sponsor. However, the Sponsor requires the investigator to permit the Sponsor, Sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The Sponsor will ensure that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information (i.e., Health Insurance Portability and Accountability Act [HIPAA]).

8.3 Administrative Matters

8.3.1 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the Investigator's Brochure and other pertinent information is confidential and remains the property of the Sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the Sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the Sponsor with all data obtained during the study.

Publication of the study results is discussed in the Clinical Study Agreement.

8.3.2 Documents and Records Related to the Clinical Study

The investigator will archive all study data (e.g., Patient Identification Code List, source data, CRFs, and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation. The investigator agrees to obtain the Sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The Sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the patients' medical records and/or study progress notes. All data will be entered on the CRFs supplied for each patient.

8.3.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments/substantial amendments and/or /non-substantial amendments. Depending on the nature of the amendment, either IRB/IEC, Competent Authority approval or notification may be required. The changes will become effective only after the approval of the Sponsor, the investigator, the regulatory authority, and the IRB/IEC (if applicable).

Amendments to this protocol must be signed by the Sponsor and the investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented which affects patient safety or the evaluation of safety, and/or efficacy. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

If there are changes to the ICF, written verification of IRB/IEC approval must be forwarded to the Sponsor. An approved copy of the new Informed Consent must also be forwarded to the Sponsor.

8.3.4 Insurance of Patients

The Sponsor has covered this study by means of an insurance of the study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's File.

8.3.5 Signatory Investigator for Clinical Study Report

ICH Efficacy guidelines 3 (ICH E3) recommend that a final study report which forms part of a marketing authorization application be signed by the representative for the Coordinating Investigator(s) or the Principal Investigator(s). The representative for the Coordinating Investigator (s) or the Principal Investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for Coordinating Investigator(s) or the Principal Investigator(s) will be selected from the participating investigators by the Sponsor prior to database lock.

9 QUALITY ASSURANCE

The Asia/ Oceania Medical Affairs Department, Astellas Pharma Singapore Pte Ltd will provide oversight of study activities that have been assigned to Sponsor's designee responsible for site management and monitoring. All study specific processes and definitions will be documented by the appointed Sponsor's designee's management group and in accordance with the Sponsor's designee's SOPs.

The Sponsor's designee will implement and maintain quality assurance and quality control (QC) systems with written SOPs to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP, Good Pharmacovigilance Practice (GPP) and applicable regulatory requirements

Details on data quality management, handling of missing data, validation and plausibility checks, query plan and data review will be described in the Sponsor's designee predefined Data Management Plan and Quality Review Plan, as agreed upon with the Sponsor. National and international data protection laws as well as regulations on interventional studies will be followed.

The Sponsor or Sponsor's designee may arrange to inspect/audit the study at any or all the investigational sites. The auditor is independent from the clinical monitoring and project management teams at the Sponsor or the Sponsor's designee. The audit may include on-site review of regulatory documents, eCRF and source documents. Direct access to these documents will be required by the auditors.

10 STUDY ORGANIZATION

A Study Steering Committee was formed whose role is to refine the design, conduct, analysis and reporting of the study. It is composed of international experts specializing in the treatment of prostate cancer. Outside experts will be designated by the Steering Committee to provide specific guidance as needed throughout the study. A separate Publication Steering Committee will be formed to oversee planning of publications related to the ELIGANT study. Publication Steering Committee membership will include at a minimum a Steering Committee representative and a representative of the Sponsor. Authorship will be based on guidelines set forth in the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors, 1997).

11 REFERENCES

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12 APPENDICES

12.1 List of stand-alone documents

Number	Document reference number	Date	Title
Appendix I	RG08029	26th Jun 2008	Tolmar Inc. ELIGARD® IB
Appendix II	APvS-T-CP01.35/9	6th Nov 2017	Astellas Always Serious Terms List

12.2 List of Excluded Concomitant Medications

1. Other LHRH analogues,
2. LHRH antagonists and other agents (approved or investigational) which are known to impact on testosterone or PSA level,
3. Ketoconazole,
4. Estrogens,
5. Herbal medications that may affect PSA levels (i.e., saw palmetto),
6. Androgens (testosterone, dihydroepiandrosterone, etc.),
7. Abiraterone,
8. Enzalutamide,
9. Chemotherapy agents including docetaxel and platinum drugs

Note: No pharmacokinetic drug-drug interaction studies have been performed with Leuprorelin (ELIGARD®). There have been no reports of any interactions of leuprorelin acetate with other medicinal product. Anti-androgen should be considered for this study.

12.3 Liver Safety Monitoring and Assessment

Any patient enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases (AT) to > 3 × upper limits of normal (ULN) (to > 5 × ULN in patients with liver metastases), or bilirubin > 2 × ULN, should undergo detailed testing for liver enzymes (including at least ALT, AST, ALP, and TBL). Testing should be repeated within 48-72 hours of notification of the test results. Patients should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST		**Total Bilirubin**
Moderate	> 3 x ULN (in patients without liver metastases), > 5 x ULN (in patients with liver metastases)	or	> 2 x ULN
Severe*	> 3 x ULN	and	> 2 x ULN

In addition, the patient should be considered to have severe hepatic abnormalities for any of the following:

ALT or AST > 8 × ULN

ALT or AST > 5 × ULN for more than 2 weeks (in the absence of liver metastases)

ALT or AST > 3 × ULN and INR > 1.5 (If international normalized ratio [INR] testing is applicable/evaluated).

ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination, and laboratory tests. The site should complete the Liver Abnormality Case Report Form (LA-CRF) that has been developed globally and can be activated for any study or appropriate document. Patients with confirmed abnormal LFT should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2-3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the patient is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology may be considered an important medical event and may be reported as an SAE. The Sponsor should be contacted and informed of all patients for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new onset-diseases should be recorded as AEs on the AE page of the eCRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Non-alcoholic steatohepatitis (NASH) is seen in obese hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating AT levels. The investigator should ensure that the medical history form captures any illness that pre-dates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including non-prescription medication, complementary and alternative medications), alcohol use, recreational drug use, and special diets. Medications, including dose, should be entered on the concomitant medication page of the eCRF. Information on alcohol, other substance use, and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents.
- Based on the patient's history, other testing may be appropriate including:
    - Acute viral hepatitis (A,B, C, D, E or other infectious agents).
    - Ultrasound or other imaging to assess biliary tract disease
    - Other laboratory tests including INR, direct bilirubin
- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Discontinuation

In the absence of an explanation for increased LFTs, such as viral hepatitis, pre-existing or acute liver disease, presence of liver metastases, or exposure to other agents associated with liver injury, the patient may be discontinued from the study. The investigator may determine that it is not in the patient's best interest to continue study enrollment. Discontinuation of treatment should be considered if:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks (in patients without liver metastases
- ALT or AST > 3 × ULN and TBL > 2 × ULN or INR > 1.5 (If INR testing is applicable/evaluated)
- ALT or AST > 5 × ULN and (TBL > 2 × ULN in patients with liver metastases)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

In addition, if close monitoring for a patient with moderate or severe hepatic laboratory tests is not possible, drug should be discontinued.

*Hy's Law Definition-Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10–50% mortality (or transplant)." The 2 "requirements" for Hy's Law are:1. Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher than 3 times the ULN ("2 x ULN elevations are too common in treated and untreated patients to be discriminating"); 2. Cases of increased bilirubin (at least 2 x ULN) with concurrent transaminase elevations at least 3 x ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's syndrome. [Temple R. Hy's law: predicting serious hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006 Apr;15(4):241-3.]

Reference

Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" issued by the United States Food and Drug Administration (FDA) on July 2009.

12.4 Common Serious Adverse Events

The following is a list of serious adverse events that the Sponsor considers to be associated with the disease state being studied. **The list does NOT change your reporting obligations or prevent the need to report an adverse event meeting the definition of an SAE as detailed in Section 5.6.2 Definition of Serious Adverse Event (SAE).** The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common serious adverse events". You are required to follow the requirements detailed in **Section 5.6.5 Reporting of Serious Adverse Events (SAE).**

Common Serious Adverse Events due to prostate cancer include:

- Urinary flow obstruction
- Hematuria
- Spinal cord compression/ Paraplegia
- Pleural effusion
- Bone fractures

12.5 EQ5D-5L Questionnaire

12.6 EORTC QLQ-PR25 Questionnaire

12.7 Protocol Amendment Summary Document

Protocol Amendment Summary Document

ISN/Protocol 7015-MA-3072

Substantial Amendment Version 2.0

18 April 2018

I. The purpose of this amendment is:

Substantial Changes
1. Update Protocol Title
DESCRIPTION OF CHANGE:
Remove the description of efficacy and quality of life from the protocol title.
RATIONALE:
The protocol is revised to reflect the primary objective of this study for establishing the safety profile of ELIGARD® in ethnic Asian prostate cancer patients.
2. Update Sample Size , Study Period and Center Numbers for the Study
DESCRIPTION OF CHANGE:
The sample size for this study is revised to approximately 107 enrolled prostate cancer patients, with 96 completed patients. The number of participating centers in the study is revised to 20 centers. The planned total duration of the study is revised to 30 months from the date of first patient enrollment until 3 months after the last dose of ELIGARD® administration. The enrollment period is revised to 12 months.
RATIONALE:
The sample size is revised based on the rationale that more than 90% of subjects will have Testosterone level of 20-50mg/dL. The original sample (N=345) will not lead to effective analysis in the study cohorts based on Testosterone levels and hence no added substantial impact with reduction in sample size. In addition, this study is not a registration study and multiple global data from LHRH analogues is available that a wider confidence interval should not have a meaningful risk. The study timeline is shortened considering 107 patients rather than 345 patients will be enrolled. The number of 20 participating sites is based on the sample size of 345 patients. However, because RA approval and EC submission for all 20 countries have been done, it has been decided to keep all 20 sites.

3. Update Table 1 Schedule of Assessments
DESCRIPTION OF CHANGE:
Add language to clarify the choices available in eCRF for the most important factors for selection of treatment, including rising PSA after definitive treatment, optimal testosterone control, quality of life, convenience of 3-monthly formulation, and other. Add language in the footnote f to clarify the Visual Analogue Scale (VAS) will only be collected if done in routine clinical practice.
RATIONALE:
The reasons for selection of treatment with ELIGARD® 22.5mg will be collected at the baseline visit. Examples for potential factors, such as rising PSA after definitive treatment, optimal testosterone control, quality of life and convenience of use, are added as a guidance in the assessment schedule table.
4. **Update Concomitant Treatment Definition**
DESCRIPTION OF CHANGE:
Include language to clarify the appropriate anti-androgen should be considered beginning at least 3 days to 4 weeks prior to ELIGARD® injection and continuing for the first 2 to 3 weeks of treatment.
RATIONALE:
The revision is to keep consistency with the following statement in Section V Flow Chart and Schedule of Assessment. Anti-androgen for at least 3 days to 4 weeks prior to the first ELIGARD® injection and continuing for the first 2 to 3 weeks of treatment should be considered.
5. Add One Additional Definition For Discontinuation
DESCRIPTION OF CHANGE:
One additional condition for discontinuation is added to define patients will be discontinued from the study in the case of patient taking prohibited medications as described in protocol Section 5.1.6 and Section 12.2.
RATIONALE:
The drugs prohibited to be used throughout the study are described in protocol Section 5.1.6 and Section 12.2. Individual patients who are enrolled in the study and take prohibited medications during the study course should be discontinued prematurely from the study.
6. Update Selection of Study Population and Inclusion Criteria

DESCRIPTION OF CHANGE:
Include wording of "and" to include patients with locally advanced prostate cancer with biochemical relapse following radical prostatectomy and radiotherapy. Include wording of "OR" to make inclusion criteria #4 and #5 as one criterion.
RATIONALE:
To include the patients with locally advanced prostate cancer with biochemical relapse following radical prostatectomy only, radiotherapy only, both radical prostatectomy and radiotherapy. The criteria of "Locally advanced prostate cancer with biochemical relapse following radical prostatectomy and/or radiotherapy" and "Hormonal treatment-naive advanced or metastatic prostate cancer patient who has not received chemotherapy and has no plans to undergo treatment with chemotherapy at study entry" are not both possible to be met in one particular patient.
7. Update Interim Analyses Cut-Off Time and Condition
DESCRIPTION OF CHANGE:
The schedule of the interim analysis is revised to be conducted when 50 of the patients complete 1 year of follow-up after the first patient is enrolled.
RATIONALE:
To specify the estimated number of patients to be included in the interim report, and to revise the criteria that patients to be analyzed will be those who complete 1 year of follow up instead of those who complete treatment, since treatment may stop for various reasons during the study.
8. Update background information for ELIGARD® Risk Management Plans (RMP)
DESCRIPTION OF CHANGE:
Add "QT prolongation" in Section 1.2 Clinical data to include major updates of ELIGARD® RMP.
RATIONALE:
The QT prolongation was added because the ELIGARD RMP was updated to version 7.0 and submitted at the end of Oct 2017 to the Health Authorities. The summary of the major updates is listed below: 1. QT prolongation was added as one of the new important identified risks.

2. The other safety concerns remained the same, including important identified risks renamed as "Transient testosterone flare", "Diabetes and hyperglycemia" & "Convulsions" which has been covered in Section 1.2 of the protocol.

Non-Substantial Changes
1. Update Contact Details of Key Sponsor's Personnel
DESCRIPTION OF CHANGE:
Include minor administrative-type changes.
RATIONALE:
To provide clarifications to the protocol and to ensure complete understanding of study procedures.
2. **Update Timeline of Study Period**
DESCRIPTION OF CHANGE:
Update timeline for each milestone of the study, including start and end of data collection, final report of study results and publication.
RATIONALE:
The study timeline is updated due to the changes of sample size from 345 to 107 enrolled patients.
3. Update Flow Chart and Schedule of Assessment
DESCRIPTION OF CHANGE:
Add language in the footnote clarifying the definition of "one month=30 days."
RATIONALE:
To provide clarifications to the protocol and to ensure complete understanding of study population

4. Minor Administrative–type Changes
DESCRIPTION OF CHANGE:
Include minor administrative-type changes, e.g., document version, format, typo, consistency, citation and reference style throughout the protocol following STL1015
RATIONALE:
To provide clarifications and writing style consistency to the protocol and to ensure complete understanding of study population
5. Update Analysis of Secondary Endpoints
DESCRIPTION OF CHANGE:
Update language to specify the measurement of time to PSA progression is calculated from date of first administration of ELIGARD® 22.5 mg to PSA progression.
RATIONALE:
Include format type changes to specify the definition for time to PSA progression.

II. Amendment Summary of Changes:

Front Page, IV Synopsis *Title of Study*
WAS:
A Phase IV Interventional Safety, Efficacy and Quality of Life Study of ELIGARD® in Prostate Cancer Patients in Asia (ELIGANT)
IS AMENDED TO:
A Phase IV Interventional Safety~~, Efficacy and Quality of Life~~ Study of ELIGARD® in Prostate Cancer Patients in Asia (ELIGANT)

II. Contact Details of Key Sponsor's Personnel
WAS:
Sponsor's personnel: 24h-Contact for Serious Adverse Events (SAEs): See Section 5.6.5 Quintiles Lifecycle Safety Email: PHV_Astellas@Quintiles.com Fax: +65 6872 8462 *Medical Monitor:* PPD *Clinical Research Contacts:* PPD PPD
IS AMENDED TO:
Sponsor's personnel: 24h-Contact for Serious Adverse Events (SAEs): See Section 5.6.5 ~~Quintiles~~ **IQVIA** Lifecycle Safety Email: ~~PHV_Astellas@Quintiles.com~~ **QLS_Eligard@quintiles.com**

Fax: +65 6872 8462 *Medical Monitor:* PPD PPD *Clinical Research Contacts:* PPD PPD PPD

IV Synopsis *Planned Study Period*
WAS:
From Q1 2017 to Q1 2020 Start of data collection:Q1 2017 End of data collection:Q1 2020 Final report of study results:Q4 2020 Publication:Q4 2021
IS AMENDED TO:
From ~~Q1 2017~~ **Q2 2017** to Q1 2020

Start of data collection: ~~Q1 2017~~ **Q2 2017** End of data collection: Q1 2020 Final report of study results: ~~Q4 2020~~ **Q3 2020** Publication: ~~Q4 2021~~ **Q3 2021**

V Flow Chart and Schedule of Assessments *Flow Chart: Footnote*
ADDED:
One month=30 days

V Flow Chart and Schedule of Assessments *Table 1 Schedule of Assessments*
WAS:
Most important factors for selection of treatment
IS AMENDED TO:
Most important factors for selection of treatment **(Rising PSA after definitive treatment, optimal testosterone control, quality of life, convenience of 3 monthly formulation, other).**

V Flow Chart and Schedule of Assessments *Table 1 Schedule of Assessments – Footnote f.*
WAS:
f. Prostate cancer status - stage of prostate cancer, bone metastasis, soft tissue disease, visceral disease, pain (using Visual Analogue Scale (VAS) 0-10), ECOG status
IS AMENDED TO:

f. Prostate cancer status - stage of prostate cancer, bone metastasis, soft tissue disease, visceral disease, pain (using Visual Analogue Scale [VAS] 0-10 **which will only be collected if done in routine clinical practice**), ECOG status

1. Introduction *1.2 Non-clinical and Clinical data*
WAS:
Decreased bone density and rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported during the post-marketing experience after the administration of GnRH agonists (0). Convulsions have also been reported in the post-marketing setting (8).
IS AMENDED TO:
Decreased bone density and rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported during post-marketing experience after the administration of GnRH agonists ~~(0)~~ **[ELIGARD local prescribing information, May 2014]**. Convulsions **and QT prolongation** have also been reported in the post-marketing setting ~~(0)~~ **[ELIGARD local prescribing information, May 2014]**.

2.2 Study Design and Dose Rationale, and IV Synopsis *2.2.1 Study Design*
WAS:
This study will be conducted in approximately 15 centers in 8 countries (Hong Kong, Indonesia, Malaysia, Philippines, Singapore, Taiwan, Thailand and Vietnam). The planned total duration of this study is 36 months from the date when the first patient is enrolled. The patient population includes male Asian patients diagnosed with prostate cancer who will receive ELIGARD® 22.5 mg (3-monthly formulation) depot formulation between the periods of Q1 2017 through Q2 2018. The enrollment period will be up to 18 months. The sample size planned for this study is approximately 345 enrolled prostate cancer patients.
IS AMENDED TO:
This study will be conducted in approximately ~~15~~ **20** centers in 8 countries (Hong Kong, Indonesia, Malaysia, Philippines, Singapore, Taiwan, Thailand and Vietnam). The planned total duration of this study is ~~36~~ **30** months from the date when the first patient is enrolled

until 3 months after the last dose of ELIGARD® 22.5 mg administration. The patient population includes male Asian patients diagnosed with prostate cancer who will receive ELIGARD® 22.5 mg (3-monthly formulation) depot formulation between the periods of ~~Q1~~**Q2** 2017 through Q3 2018. The enrollment period will be up to ~~18~~ **12** months. The sample size planned for this study is approximately ~~345~~ **107** enrolled prostate cancer patients.

3 Study Population and IV Synopsis *3.1 Selection of Study Population*
WAS:
This study is designed for male patients with: • locally advanced prostate cancer with biochemical relapse following radical prostatectomy or radiotherapy; and • hormonal treatment-naive advanced or metastatic prostate cancer
IS AMENDED TO:
This study is designed for male patients with: • **L**ocally advanced prostate cancer with biochemical relapse following radical prostatectomy **and**/or radiotherapy (see inclusion criteria 4) • **H**ormonal treatment-naive advanced or metastatic prostate cancer

3 Study Population and IV Synopsis *3.2 Inclusion Criteria #1, 2, 4, 5*
WAS:
6. Being ethnic Asian male patient above 18 years of age 7. Being willing and able to provide written informed consent 4. Locally advanced prostate cancer with biochemical relapse following radical prostatectomy or radiotherapy. Biochemical relapse (1) is defined as: • PSA > 2 ng/mL following radiotherapy, or • Two consecutive PSA values > 0.2 ng/mL and rising above the nadir following radical prostatectomy

5. Hormonal treatment-naive advanced or metastatic prostate cancer patient who has not received chemotherapy and has no plans to undergo treatment with chemotherapy at study entry. 6. Patient who indicates that once the study is completed, he expects having access to androgen deprivation therapy (ADT), either medical or surgical, within the local healthcare system (either through public/ private health insurance or out of pocket payment).
IS AMENDED TO:
1. ~~Being~~ Ethnic Asian male patient above 18 years of age 2. ~~Being~~ Willing and able to provide written informed consent 4. Locally advanced prostate cancer with biochemical relapse following radical prostatectomy **and**/or radiotherapy. Biochemical relapse **[Mottet et al, 2006]** is defined as: • PSA > 2 ng/mL following radiotherapy, or • Two consecutive PSA values > 0.2 ng/mL and rising above the nadir following radical prostatectomy **OR** Hormonal treatment-naive advanced or metastatic prostate cancer patient who has not received chemotherapy and has no plans to undergo treatment with chemotherapy at study entry. 5. Patient who indicates that once the study is completed, he expects having access to androgen deprivation therapy (ADT), either medical or surgical, within the local healthcare system (either through public/ private health insurance or out of pocket payment).

IV Synopsis *Concomitant medication restrictions or requirements*
WAS:
Bicalutamide 50 mg O.D. or a similar anti-androgen is an allowed concomitant medication for flare prevention only. The anti-androgen for flare prevention should be considered beginning 3 days prior to leuprorelin therapy and continuing for the first two to three weeks of treatment.

IS AMENDED TO:
Bicalutamide 50 mg O.D. or a similar anti-androgen is an allowed concomitant medication for flare prevention only. The anti-androgen for flare prevention should be considered beginning **at least** 3 days **to 4 weeks** prior to ~~**leuprorelin therapy**~~ **the first ELIGARD® injection** and continuing for the first **2** ~~**two**~~ to **3** ~~**three**~~ weeks of treatment.

5 Treatments and Evaluation *5.1.3 Previous and Concomitant Treatment*
WAS:
Bicalutamide 50 mg O.D. or a similar anti-androgen is an allowed concomitant medication for flare prevention only. Additional administration of an appropriate anti-androgen should be considered beginning three days prior to ELIGARD treatment and continuing for the first two to three weeks of treatment to avoid any flare reaction.
IS AMENDED TO:
Bicalutamide 50 mg O.D. or a similar anti-androgen is an allowed concomitant medication for flare prevention only. Additional administration of an appropriate anti-androgen should be considered beginning **at least** ~~**three-**~~**3** days **to 4 weeks** prior to ~~**ELIGARD treatment**~~ **the first ELIGARD® injection** and continuing for the first ~~**two**~~ **2** to ~~**three**~~ **3** weeks of treatment to avoid any flare reaction.

5 Treatments and Evaluation, and IV Synopsis *5.1.6 Restrictions During the Study*
WAS:
The following drugs are prohibited to be used throughout the study (see Section 12.2): 10. other LHRH analogues,
IS AMENDED TO:
The following drugs are prohibited to be used throughout the study (see Section 12.2): 1. ~~o~~**O**ther LHRH analogues,

5.6 Adverse Events and Other Safety Aspects *5.6.1 Definition of Adverse Events*
WAS:

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, electroniccardiogram [ECG] data, physical exam) should be defined as an AE only if the abnormality meets 1 of the following criteria:
IS AMENDED TO:
An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ~~electroniccardiogram~~ **electrocardiogram** [ECG] data, physical exam) should be defined as an AE only if the abnormality meets 1 of the following criteria:

6 Discontinuation *6.1 Discontinuation of Individual Patients*
ADDED:
A patient will be discontinued from the study in the case of: **11. Patient takes prohibited medications as described in Section 5.1.6 and Section 12.2**

7 Statistical Methodology and IV Synopsis
WAS:
Data analysis will be performed by the designated CRO in accordance with the CRO's SOPs for statistics and clinical programming with oversight from the Global Data Science Department of the Sponsor. *7.1 Sample Size* This study targets to enroll approximately 345 prostate cancer patients. The sample size was calculated based on the estimated percentage of ELIGARD®-related AEs, as well as the desired width of its 95% Confidence Interval (CI). Prior clinical studies on ELIGARD® have shown an ELIGARD®-related AEs rate of around 50% of patients during a six-month treatment period (12,13). Considering the treatment duration will be 18 months in this study, the percent of patients that experienced ELIGARD®-related AEs is estimated to be 70% for sample size calculation. A sample size of 313 completed patients is sufficient for estimating a Wald 95% CI with a width of 10% (+/- 5% from the middle), based on a finite population correction, with factor N=10,000. Therefore, the total sample size of this study, assuming a drop-out rate of 10% is 345 patients.

PASS 14 Power Analysis and Sample Size Software (2015) version number 14.0.2 was used in the sample size calculation (NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass).

IS AMENDED TO:

Data analysis will be performed by the designated CRO in accordance with the CRO's SOPs for statistics and clinical programming ~~with oversight from the Global Data Science Department of the Sponsor~~ **with oversight from MA Statistics of the Sponsor**.

7.1 Sample Size

This study targets to enroll approximately ~~345~~**107** prostate cancer patients.
The sample size was calculated based on the estimated percentage of ELIGARD® -related AEs, as well as the desired width of its 95% Confidence Interval (CI). Prior clinical studies on ELIGARD® have shown an ELIGARD®-related AEs rate of around 50% of patients during a six-month treatment period ~~(12,13).~~ **[ELIGARD Investigator's Brochure, June 2008; Tombal & Berges, 2007].** ~~Considering the treatment duration will be 18 months in this study, the percent of patients that experienced ELIGARD® related AEs is estimated to be 70% for sample size calculation~~ **With the assumption that the percentage of ELIGARD®-related AEs will be 50%, a** sample size of ~~313~~ **96** completed patients is sufficient for estimating a Wald 95% CI with a width of ~~10%~~**20%** (+/- ~~5%~~**10%** from the middle), based on a finite population correction, with factor N=10,000.
Therefore, total sample size of this study, assuming a drop-out rate of 10%, is ~~345~~ **107** patients.
PASS 14 Power Analysis and Sample Size Software (2015) version number 14.0.2 was used in the sample size calculation.

7 Statistical Methodology and IV Synopsis
7.4.2 Analysis of Secondary Endpoints

WAS:

Descriptive statistics will be presented for the following:

- Percentage of patients with Testosterone <20, 20-50 and >50 ng/dL at one year and at 1.5 years
- Time to PSA progression: PSA progression as the date that a 25% or greater increase and an absolute increase of 2 ng/mL or more from the nadir is documented, which is:
    - Confirmed by a second value obtained 3 or more weeks later

○ Time to PSA progression is calculated from the date of first administration of ELIGARD 22.5mg. ○ If not done based on standard clinical practice, the confirmatory PSA measurement will be performed at the next routine study visit.
IS AMENDED TO:
Descriptive statistics will be presented for the following: • Percentage of patients with Testosterone <20, 20-50 and >50 ng/dL at 1 year and at 1.5 years • Time to PSA progression: **calculated from date of first administration of ELIGARD 22.5mg to PSA progression** • PSA progression ~~as the date that a~~ **will be defined as a** 25% or greater increase and an absolute increase of 2 ng/mL or more from the nadir is documented, which is ○ Confirmed by a second value obtained 3 or more weeks later ○ ~~Time to PSA progression is calculated from the date of first administration of ELIGARD 22.5mg~~ ○ If not done based on standard clinical practice, the confirmatory PSA measurement will be performed at the next routine study visit.

7 Statistical Methodology *7.2.1 Full Analysis Set (FAS)*
WAS:
The full analysis set (FAS) will consist of all patients who are enrolled and receive at least one dose of study drug and have at least one post baseline measurement. This will be the primary analysis set for efficacy analyses.
IS AMENDED TO:
The full analysis set (FAS) will consist of all patients who are enrolled and receive at least ~~one~~ **1** dose of study drug and have at least ~~one~~ **1** post baseline measurement **of PSA and testosterone levels**. This will be the primary analysis set for efficacy analyses.

7 Statistical Methodology and IV Synopsis *7.7 Interim Analyses*
WAS:
A minimum of one interim analysis will be conducted at 21 months after the first patient is enrolled for that half of patients will complete one year of treatment.
IS AMENDED TO:
A minimum of 1 interim analysis will be conducted ~~at 21 months after the first patient is enrolled for that half of patients will complete one year of treatment.~~**when 50 patients complete 1 year of follow-up.**

8 Procedure for Clinical Study Quality Control *8.1.1 Data Collection*
WAS:
The investigator or site designee will enter the questionnaire data directly into the EDC system. The monitor will collect the questionnaires, and submit them to the Sponsor or designee, ensuring a copy remains at site.
IS AMENDED TO:
The investigator or site designee will enter the questionnaire data directly into the EDC system. **The paper questionnaires will be kept at sites.** ~~The monitor will collect the questionnaires, and submit them to the Sponsor or designee, ensuring a copy remains at site.~~

11 REFERENCES
WAS:
The references were numbered and in order of citation in the text
IS AMENDED TO:
The references were listed alphabetically by first author, as per STL-1051

12 APPENDICES *12.1 List of stand-alone documents*
WAS:
Appendix II APvS-T-CP01.35/4 2nd Nov 2015 Astellas Always Serious Terms List
IS AMENDED TO:
Appendix II APvS-T-CP01.35/**49** ~~2nd~~ **6th** Nov ~~2015~~ **2017** Astellas Always Serious Terms List
12.7 Protocol Amendment Summary Document
ADDED:
Section12.7 Protocol Amendment Summary Document

13 SPONSOR'S SIGNATURES
WAS:

13.1 Protocol Authors

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Quintiles

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13.1 PROTOCOL AUTHORS

13 SPONSOR'S SIGNATURES

13.1 PROTOCOL AUTHORS

13 SPONSOR'S SIGNATURES

13.1 PROTOCOL AUTHORS

13.2 PROTOCOL APPROVED BY

13.2 PROTOCOL APPROVED BY

Protocol Approval Committee
PPD

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Protocol Approval Committee