China ARCHES: A Multicenter, Phase 3, Randomized, Double-blind, Placebo-controlled Efficacy and Safety Study of Enzalutamide Plus Androgen Deprivation Therapy (ADT) Versus Placebo Plus ADT in Chinese Patients with Metastatic Hormone Sensitive Prostate Cancer (mHSPC)

ISN/Protocol 9785-CL-0336

Version 5.0

Incorporating Substantial Amendment 4

06 Jan 2023

Sponsor:

Astellas Pharma China, Inc (ACN)
27th Floor, Beijing IFC Tower, NO.8, Jianguomenwai Avenue, Chaoyang District, Beijing 100022, P.R.C

Protocol History:
Version 1.0 [14 Sep 2018]
Version 1.1 Non-substantial Amendment 1 [24 Apr 2019]
Version 2.0 Incorporating Substantial Amendment 1 [21 May 2020]
Version 3.0 Incorporating Substantial Amendment 2 [27 Sep 2021]
Version 4.0 Incorporating Substantial Amendment 3 [20 Jul 2022]

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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].

2. INVESTIGATOR'S SIGNATURE

China ARCHES: A Multicenter, Phase 3, Randomized, Double-blind, Placebo-controlled Efficacy and Safety Study of Enzalutamide Plus Androgen Deprivation Therapy (ADT) Versus Placebo Plus ADT in Chinese Patients with Metastatic Hormone Sensitive Prostate Cancer (mHSPC)

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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 International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and applicable local regulations. I will also ensure that Subinvestigator(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

24-hour Contact for Serious Adverse Events (SAEs) See [Section 5.5.5]	PPD Development Medical Department - Oncology Astellas Pharma China, Inc. PPD **Fax the SAE Worksheet to:** Astellas Pharma Global Development Inc. Pharmacovigilance **North America fax number: 1-888-396-3750** **North America alternate fax number: 1-847-317-1241** **International fax number: +44-800-471-5263** **E-mail: safety-us@astellas.com** **Copy: acn_pv@astellas.com**
Medical Monitor/Medical Expert:	PPD, Development Medical Department - Oncology Astellas Pharma China, Inc. PPD
Clinical Research Contacts:	PPD Development Clinical Department Astellas Pharma China, Inc. PPD

- CONFIDENTIAL -

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Substantial Amendment 3	20 Jul 2022
Substantial Amendment 2	27 Sep 2021
Substantial Amendment 1	21 May 2020
Non-substantial Amendment 1	24 Apr 2019
Original Protocol	14 Sep 2018

Protocol 9785-CL-0336: China ARCHES: A Multicenter, Phase 3, Randomized, Double-blind, Placebo-controlled Efficacy and Safety Study of Enzalutamide Plus Androgen Deprivation Therapy (ADT) Versus Placebo Plus ADT in Chinese Patients with Metastatic Hormone Sensitive Prostate Cancer (mHSPC)

Amendment 4 [Substantial] 06-Jan-2023

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The purpose of this amendment is to update the design and details for the open-label phase. If results from China ARCHES demonstrate that enzalutamide plus androgen deprivation therapy (ADT) meets the protocol defined criteria for superiority in delaying prostate-specific antigen (PSA) progression compared with placebo plus ADT, open-label enzalutamide should be offered as a treatment option to eligible subjects currently receiving placebo after the sponsor's formal determination on study-wide unblinding.

Summary of Changes

Substantial Changes

Section Number	Description of Change	Brief Rationale
Synopsis Flow Chart Table 1	Updated the design for the open-label phase. The corresponding details in the flow chart, schedule of assessment, inclusion criteria, exclusion criteria and statistical methods were also updated.	If results from China ARCHES demonstrate that enzalutamide plus ADT meets the protocol defined

Section Number	Description of Change	Brief Rationale
Section 2.2.1 Section 12.10	**Before the sponsor's formal determination on study-wide unblinding,** open-label enzalutamide will be supplied for free to the subjects in placebo arm who remain on study treatment until confirmed radiographic disease progression and in the judgement of the investigator who is necessary to initiate the next course of therapy till next disease progression based on the subject's informed consent. **If the study results in a positive outcome and after the sponsor's formal determination on study-wide unblinding via written notice to study sites, open-label enzalutamide will be supplied for free to the subjects in both enzalutamide and placebo arms who remain on study treatment.**	criteria for superiority in delaying PSA progression compared with placebo plus ADT, open-label enzalutamide should be offered as a treatment option to eligible subjects currently receiving placebo after the sponsor's formal determination on study-wide unblinding.

Non-substantial Changes

Section Number	Description of Change	Brief Rationale
Synopsis	The planned study period is extended from the third quarter of 2023 to the fourth quarter of 2025.	The study timeline has been extended according to the actual status of the study.
Synopsis Flow Chart Table 1 Section 2.2.1 Section 5.3.1.2	Updated the PSA and radiographic assessment schedule details for subjects who discontinue study treatment without radiographic progression. Subjects who discontinue study treatment without radiographic progression will continue to follow the PSA and radiographic assessment schedule until confirmed radiographic disease progression event **or the required number of PSA progression events for the final analysis is reached**.	For correction, to be consistent with the other parts of the protocol.
Synopsis Section 2.3.1 Section 7.1	Updated the definition of PSA progression in the primary endpoint. Time to PSA progression: **PSA progression is defined as a ≥ 25% increase and an absolute increase of ≥ 2 µg/L (2 ng/mL) above the nadir (i.e., lowest PSA value observed post baseline or at baseline), which is confirmed by a second consecutive value at least 3 weeks later.** ~~(≥ 2 ng/mL)~~ (Prostate Cancer Clinical Trials Working Group 3 criteria) (tested by central laboratory)	To add the full definition of the primary endpoint to be consistent with the other parts of the protocol.

Section Number	Description of Change	Brief Rationale
Table 1	Added a footnote for the assessments on Day 1. **All the assessments on Day 1 need to be performed before treatment.**	To clarify the assessments should be performed before treatment.
Table 1 Section 5.5.1 Section 5.5.5 Table 4	Updated the period for adverse event reporting. AE collection begins after the signing of the informed consent **for the double-blind period** and will be collected until **30 days after the last dose of study drug (including the double-blind period and open-label phase if applicable), or initiation of a new therapy for prostate cancer,** ~~subject is determined to have initiation of new therapy for prostate cancer, or 30 days after the last dose of study drug,~~ or the subject is determined to be a screen failure, whichever occurs first.	To clarify the period for adverse event collection, indicate the study drug taken during the open-label phase is included for the criteria of "until 30 days after the last dose of study drug".
Table 1 Section 5.5.1 Section 5.5.5 Table 4	Updated the details for adverse event reporting. **During the post treatment follow-up period, only symptomatic skeletal events need to be reported.**	To clarify to the investigator regarding how and where to report symptomatic skeletal event during the post-treatment follow-up period, which was not clearly stated in the protocol in the previous version.
Section 1.3	Updated the key safety information for study drug according to the latest version of investigator brochure.	To include the latest safety information since the last version of the protocol.
Section 5.1.4	Updated the details for treatment compliance. If compliance **per visit** is less than 80% **or higher than 120% of the planned dosage**, and study drug was not withheld and there were no study drug reductions, the investigator or designee is to counsel the subject on the importance of taking the study drug.	To update the range for treatment compliance to be consistent with the protocol deviation specification and the study practice.
Across the protocol amendment	Included minor administrative-type changes, e.g., typos, format, numbering, consistency throughout the protocol, including an update on the contact information for study personnel.	To provide clarifications to the protocol and to ensure complete understanding of study procedures.

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
ACN	Astellas Pharma China, Inc
ADT	androgen deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
APGD	Astellas Pharma Global Development, Inc
AR	androgen receptor
AST	aspartate aminotransferase
BHA	butylated hydroxyanisole
BHT	butylated hydroxytoluene
BPI-SF	Brief Pain Inventory-Short Form
CLCR	creatinine clearance
CRF	case report form
CRPC	castration-resistant prostate cancer
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EQ-5D-5L	EuroQol Group-5 Dimension-5 Level Instrument
DAC	Data Analysis Center
FACT-P	Functional Assessment of Cancer Therapy-Prostate
GABA	γ-aminobutyric acid
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HDPE	high-density polyethylene
HR	hazard ratio
IA	Interim analysis
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISN	International study number
ITT	Intent-to-treat
LA-CRF	liver abnormality case report form
LFT	liver function test
LHRH	luteinizing hormone-releasing hormone
LHRHA	luteinizing hormone-releasing hormone analogue
mCRPC	metastatic castration-resistant prostate cancer
mHSPC	metastatic hormone sensitive prostate cancer
MRI	magnetic resonance imaging

Abbreviations	Description of abbreviations
NASH	nonalcoholic steatohepatitis
NCI	National Cancer Institute
NSAA	nonsteroidal antiandrogen
ORR	objective response rate
OS	overall survival
P-gp	P-glycoprotein
PRES	posterior reversible encephalopathy syndrome
PSA	prostate-specific antigen
PSADecR	rate of PSA decline to < 2ng/mL
QLQ-PR25	Quality of Life Prostate-specific Questionnaire
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	radiographic progression-free survival
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
SOP	standard operating procedure
SSE	symptomatic skeletal event
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
TTNAnti	time to initiation of a new antineoplastic therapy
TTPP	time to PSA progression
ULN	upper limit of normal

Definition of Key Study Terms

Terms	Definition of terms
Baseline	Observed values/findings that are regarded observed starting point for comparison.
Enroll	To register or enter into a clinical trial. NOTE: Once a subject has been enrolled, the clinical trial protocol applies to the subject.
Intervention	The drug, therapy or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a study (e.g., health-related quality of life, efficacy, safety and pharmacoeconomics).
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test drug or comparative drug (sometimes without randomization) is usually given to a subject, and continues until the last assessment after completing administration of the test drug or comparative drug.
Postinvestigational period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period.
Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Screen failure	Potential subject who did not meet 1 or more criteria required for participation in a trial.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screening period	Period of time before entering the investigational period, usually from the time of starting a subject signing consent until just before the test drug or comparative drug (sometimes without randomization) is given to a subject.
Study period	Period of time from the first site initiation date to the last site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

IV. SYNOPSIS

Date and Version # of Protocol Synopsis:	06 Jan 2023, Version 5.0
Sponsor: Astellas Pharma China, Inc (ACN)	**Protocol Number:** 9785-CL-0336
Name of Study Drug: Enzalutamide	**Phase of Development:** Phase 3
Title of Study: China ARCHES: A Multicenter, Phase 3, Randomized, Double-blind, Placebo-controlled Efficacy and Safety Study of Enzalutamide Plus Androgen Deprivation Therapy (ADT) Versus Placebo Plus ADT in Chinese Patients with Metastatic Hormone Sensitive Prostate Cancer (mHSPC)	
Planned Study Period: From 3Q2019 to 4Q2025	

Study Objective(s):

The objective of this phase 3 study is to evaluate the efficacy and safety of enzalutamide plus androgen deprivation therapy (ADT) versus placebo plus ADT in Chinese subjects with metastatic hormone sensitive prostate cancer (mHSPC).

Primary Objective

- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by time to prostate-specific antigen (PSA) progression

Secondary Objectives

- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by radiographic progression-free survival (rPFS)
- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by time to first Symptomatic Skeletal Event (SSE)
- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by time to castration resistance
- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by PSA response (≥ 50%)
- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by PSA response (≥ 90%)
- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by time to start of new antineoplastic therapy
- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by PSA undetectable rate (< 0.2 ng/mL)
- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by objective response rate (ORR)

Exploratory Objectives

- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by Quality of Life (QoL) (as measured by Quality of Life Prostate-specific Questionnaire [QLQ-PR25] / Functional Assessment of Cancer Therapy-Prostate [FACT-P] and EuroQol Group-5 Dimension-5 Level Instrument [EQ-5D-5L])

- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by worsening of pain (as measured by Brief Pain Inventory-Short Form [BPI-SF])

Safety Objective

- To determine the safety of enzalutamide plus ADT as compared to placebo plus ADT

Planned Total Number of Study Centers and Location(s):
Approximately 30 centers in China

Study Population:
The study population will consist of Chinese subjects with mHSPC.

Number of Subjects to be Randomized:
Approximately 180 Chinese subjects

Study Design Overview:
This is a multicenter phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of enzalutamide plus ADT versus placebo plus ADT in Chinese subjects with mHSPC.

Approximately 180 Chinese subjects will be randomized centrally to enzalutamide plus ADT or placebo plus ADT (2:1), and the randomization will be stratified by volume of disease (low versus high) and prior docetaxel therapy for prostate cancer (no prior docetaxel, prior docetaxel). High volume of disease is defined as metastases involving the viscera or, in the absence of visceral lesions, there must be 4 or more bone lesions, at least 1 of which must be in a bony structure beyond the vertebral column and pelvic bone. Prior docetaxel therapy is defined as 1 or more cycles of docetaxel but no more than 6 cycles. Re-screening may be allowed once after screening failure upon discussion with the medical monitor.

Study drug therapy should be continued as long as the subject is tolerating the study drug and continues ADT until radiographic disease progression is documented as outlined in the table below or starting another investigational agent or new therapy for treatment of prostate cancer. It is recommended that subjects remain on study treatment until confirmed radiographic disease progression. Subjects who discontinue study treatment without radiographic progression will continue to follow the PSA and radiographic assessment schedule until confirmed radiographic disease progression event or the required number of PSA progression events for the final analysis is reached. In the judgment of the Investigator, for subjects who discontinue study treatment with confirmed PSA progression, blinding should be maintained until confirmed radiographic disease progression. In consultation with the medical monitor, unblinding of the study treatment assignment may be performed after radiographic progression if the subject discontinues from the study treatment and in the judgement of the investigator this information is necessary to determine the next course of therapy. Before the sponsor's formal determination on study-wide unblinding, open-label enzalutamide will be supplied for free to the subjects in placebo arm who remain on study treatment until confirmed radiographic disease progression and in the judgement of the investigator who is necessary to initiate the next course of therapy till next disease progression based on the subject's informed consent. If the study results in a positive outcome and after the sponsor's formal determination on study-wide unblinding via written notice to study sites, open-label enzalutamide will be supplied for free to the subjects in both enzalutamide and placebo arms who remain on study treatment.

Study films (computed tomography [CT]/magnetic resonance imaging [MRI] and bone scan) should be read on site and also be submitted in digital format to the Sponsor-designated facility in case

independent central review is required after the end of study. Each site should ideally designate the same reader who will evaluate the images for any one subject for the duration of the trial.

Radiographic disease progression is defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 for soft tissue disease or the appearance of 2 or more new lesions on bone scan. The documentation and confirmation required for the determination of radiographic progression is listed in the following table.

Protocol-specified Documentation for Radiographic Evidence of Disease Progression

Date Progression Detected (Visit)†	Criteria for Progression	Criteria for Confirmation of Progression (Requirement and Timing)	Criteria for Documentation of Disease Progression on Confirmatory Scan
Week 13	Bone lesions: ≥ 2 new lesions compared to **baseline** bone scan	Timing: ≥ 6 weeks after progression identified or at week 25 visit	≥ 2 new bone lesions on bone scan compared to week 13 scan (≥ 4 new lesions compared to **baseline** bone scan)
	Soft tissue lesions: progressive disease on CT or MRI by RECIST v1.1	No confirmatory scan required for soft tissue disease progression	Not applicable
Week 25 or Later	Bone lesions: ≥ 2 new lesions on bone scan compared to best response on treatment	No confirmatory scan required	Not applicable
	Soft tissue lesions: progressive disease on CT or MRI by RECIST v1.1	No confirmatory scan required for soft tissue disease progression	Not applicable

CT: computed tomography; MRI: magnetic resonance imaging; RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1

† Progression detected by bone scan at an unscheduled visit prior to week 25 will require the same criteria for documentation of disease progression as week 13 with a confirmatory scan at least 6 weeks later or at the next scheduled scan.

An Independent Data Monitoring Committee (IDMC) will assess the efficacy of the study treatment(s) at a planned interim analysis, and safety data will also be considered when IDMC makes recommendations based on the efficacy data from the benefit-risk perspective.

The following assessments of prostate cancer status will be collected during the course of the study: PSA, soft tissue disease on CT scan or on MRI, bone disease on radionuclide bone scans, EQ-5D-5L, QLQ-PR25, FACT-P for QoL and BPI-SF for pain symptom assessment.

Throughout the study, safety and tolerability will be assessed by the recording of adverse events, vital signs, physical examinations, 12-lead electrocardiograms (ECGs), and safety laboratory evaluations.

Subjects will have a safety follow-up visit 30 days after their last dose of study drug or prior to initiation of another investigational agent or new therapy for prostate cancer, whichever occurs first.

The Sponsor will monitor study enrollment for proportion of subjects enrolled with a history of prior docetaxel treatment, and may either change the sample size, or cap the number of subjects who received prior docetaxel to ensure that the primary endpoint is not driven either by the subjects who received prior docetaxel, or by the subjects who did not receive prior docetaxel.

Inclusion/Exclusion Criteria:

Inclusion:

Subject is eligible for the study if all of the following apply:

1. Institutional Review Board (IRB)-/Independent Ethics Committee (IEC)-approved written informed consent and privacy language as per national regulations must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is considered an adult according to local regulation at the time of signing informed consent.
3. Subject is diagnosed with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, signet cell or small cell histology.
4. Subject has metastatic prostate cancer documented by positive bone scan (for bone disease) or measurable metastatic lesions on CT or MRI scan (for soft tissue). Subjects whose disease spread is limited to regional pelvic lymph nodes are not eligible.
5. Once randomized at day 1, subject must maintain ADT with an LHRH agonist or antagonist during study treatment or have a history of bilateral orchiectomy (i.e., medical or surgical castration).
6. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at screening.
7. Subject has an estimated life expectancy of ≥ 12 months as assessed by the investigator.
8. Subject is able to swallow the study drug and comply with study requirements.
9. A sexually active male subject with female partner(s) who is of childbearing potential is eligible if:
    - Agrees to use a male condom starting at screening and continue throughout the study treatment and for at least 3 months after the last dose of study drug. If the male subject has not had a vasectomy or is not sterile at least 6 months prior to screening as defined below his female partner(s) is utilizing 1 form of highly effective birth control* per locally accepted standards starting at screening and continue throughout study treatment and for at least 3 months after the male subject receives his last dose of study drug.

*Highly effective forms of birth control include:

- Consistent and correct usage of established hormonal contraceptives that inhibit ovulation
- Established intrauterine device (IUD) or intrauterine hormone releasing system (IUS).
- Bilateral tubal occlusion
- Vasectomy (A vasectomy is a highly effective contraception method provided the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used)
- Male is sterile due to a bilateral orchiectomy or radical cystoprostatectomy/removal of seminal vesicles
- Sexual Abstinence is considered a highly effective method only if defined as refraining from heterosexual activity during the entire period of risk associated with the study drug.

The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant

10. Subject must agree to abstinence or use a condom throughout the study period and for at least 3 months after the last dose of study drug if engaging in sexual intercourse with a pregnant or breastfeeding partner(s).
11. Subject must agree not to donate sperm from first dose of study drug through 3 months after the last dose of study drug.
12. Subject agrees not to participate in another interventional study while on treatment.

Waivers to the inclusion criteria will NOT be allowed.

Exclusion:

Subject will be excluded from participation if any of the following apply:

1. Subject has received any prior pharmacotherapy, radiation therapy or surgery for metastatic prostate cancer (the following exceptions are permitted):
    - Up to 3 months of ADT with luteinizing hormone-releasing hormone (LHRH) agonists or antagonists or orchiectomy with or without concurrent antiandrogens prior to day 1, with no radiographic evidence of disease progression or rising PSA levels prior to day 1;
    - Subject may have 1 course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease if it was administered at least 4 weeks prior to day 1;
    - Up to 6 cycles of docetaxel therapy with final treatment administration completed within 2 months of day 1 and no evidence of disease progression during or after the completion of docetaxel therapy;
    - Up to 6 months of ADT with LHRH agonists or antagonists or orchiectomy with or without concurrent antiandrogens prior to day 1 if subject was treated with docetaxel, with no radiographic evidence of disease progression or rising PSA levels prior to day 1;
    - Prior ADT given for < 39 months in duration and > 9 months before randomization as neoadjuvant/adjuvant therapy.
2. Subject had a major surgery within 4 weeks prior to day 1.
3. Subject received treatment with 5-α reductase inhibitors (finasteride, dutasteride) within 4 weeks prior to day 1.
4. Subject received treatment with estrogens, cyproterone acetate or androgens within 4 weeks prior to day 1.
5. Subject received treatment with systemic glucocorticoids greater than the equivalent of 10 mg per day of prednisone within 4 weeks prior to day 1, intended for the treatment of prostate cancer.
6. Subject received treatment with herbal medications that have known hormonal antiprostate cancer activity and/or are known to decrease PSA levels within 4 weeks prior to day 1.
7. Subject received prior aminoglutethimide, ketoconazole, abiraterone acetate or enzalutamide for the treatment of prostate cancer or participation in a clinical study of an investigational agent that inhibits the androgen receptor or androgen synthesis (e.g., TAK-700, ARN-509, ODM-201).
8. Subject received investigational agent within 4 weeks prior to day 1.
9. Subject has known or suspected brain metastasis or active leptomeningeal disease.
10. Subject has a history of another invasive cancer within 3 years of screening, with the exception of fully treated cancers with a remote probability of recurrence based on investigator assessment.

11. Subject has absolute neutrophil count < 1500/μL, platelet count < 100000/μL or hemoglobin < 10 g/dL (6.2 mmol/L) at screening. NOTE: May not have received any growth factors within 7 days or blood transfusions within 28 days prior to the hematology values obtained at screening.
12. Subject has total bilirubin ≥ 1.5 × the upper limit of normal (except subjects with documented Gilbert's disease), or alanine aminotransferase or aspartate aminotransferase ≥ 2.5 × the upper limit of normal at screening.
13. Subject has creatinine > 2 mg/dL (177 μmol/L) at screening.
14. Subject has albumin < 3.0 g/dL (30 g/L) at screening.
15. Subject has a history of seizure or any condition that may predispose to seizure (e.g., prior cortical stroke or significant brain trauma, brain arteriovenous malformation).
16. Subject has history of loss of consciousness or transient ischemic attack within 12 months prior to day 1.
17. Subject has clinically significant cardiovascular disease, including the following:
    - Myocardial infarction within 6 months prior to screening;
    - Unstable angina within 3 months prior to screening;
    - New York Heart Association class III or IV congestive heart failure or a history of New York Heart Association class III or IV congestive heart failure unless a screening echocardiogram or multigated acquisition scan performed within 3 months before the randomization date demonstrates a left ventricular ejection fraction ≥ 45%;
    - History of clinically significant ventricular arrhythmias (e.g., sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes);
    - History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place;
    - Hypotension as indicated by systolic blood pressure < 86 mm Hg at screening;
    - Bradycardia as indicated by a heart rate of ≤ 45 beats per minute on the screening ECG;
    - Uncontrolled hypertension as indicated by a minimum of 2 consecutive blood pressure measurements showing systolic blood pressure > 170 mm Hg or diastolic blood pressure > 105 mm Hg at screening.
18. Subject has gastrointestinal disorder affecting absorption.
19. Subject has any concurrent disease, infection or comorbid condition that interferes with the ability of the subject to participate in the study, which places the subject at undue risk or complicates the interpretation of data in the opinion of the investigator.
20. Subject received bisphosphonates or denosumab within 2 weeks prior to day 1 unless administered at stable dose or to treat diagnosed osteoporosis.
21. Subject has shown a hypersensitivity reaction to the active pharmaceutical ingredient or any of the study capsule components, including Labrasol®, butylated hydroxyanisole (BHA), and butylated hydroxytoluene (BHT).

Waivers to the exclusion criteria will NOT be allowed.

Investigational Product(s):

Enzalutamide 40 mg capsule

Dose(s):

160 mg once daily

Mode of Administration:
Oral, with or without food

Comparative Drug(s):
Placebo capsules that are identical in appearance to enzalutamide will be administered in the same manner and frequency as enzalutamide.

Enzalutamide Dose Reduction / Dose Adjustment
Subjects who experience a grade 3 or higher toxicity that is attributed to the study drug and cannot be ameliorated by the use of adequate medical intervention and/or dose reduction may interrupt study drug treatment for 1 week or until the toxicity grade improves to grade 2 or lower in severity. Study drug may be restarted at the original dose (160 mg/day) or a reduced dose (120 mg or 80 mg/day). If restarted at a lower dose or if interrupted for > 2 weeks, the Medical Monitor must be consulted.

Other Treatment for Prostate Cancer during the Study:
ADT (either bilateral orchiectomy or LHRH agonist/antagonist) will be maintained during study treatment. LHRH agonist/antagonist will be provided from the site's pharmacy stock and administered in accordance with the prescribing information.

Concomitant Medication Restrictions or Requirements:

Required Concomitant Treatment

All subjects will be required to maintain ADT during study treatment, either using an LHRH agonist/antagonist or having a history of bilateral orchiectomy.

Prohibited Concomitant Treatments

The following medications are prohibited within 4 weeks of day 1 and during the study treatment period:

- 5 α-reductase inhibitors (finasteride, dutasteride);
- Estrogens;
- Cyproterone acetate, megestrol acetate;
- Biologic or other agents with antitumor activity against prostate cancer (with the exception of those therapies identified in exclusion criterion No. 1);
- Systemic glucocorticoids greater than the equivalent of 10 mg per day of prednisone intended for the treatment of prostate cancer;
- Herbal medications that have known hormonal antiprostate cancer activity and/or are known to decrease PSA levels (i.e., saw palmetto);
- Androgens (testosterone, dihydroepiandrosterone, etc.);
- Investigational agents.

In addition, bisphosphonates and denosumab are prohibited unless stabilized for 2 weeks prior to randomization and held constant, as tolerated, throughout study treatment or administered for diagnosis of osteoporosis.

Enzalutamide Drug Interaction

There is a potential for enzalutamide to affect exposures to other medicinal products, or for other medicinal products to affect exposure to enzalutamide:

- Strong cytochrome P450 (CYP) 2C8 inhibitors (e.g., gemfibrozil) are to be avoided. If subject must be coadministered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily. If coadministration of the strong inhibitor is discontinued, the enzalutamide

dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.

- Strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin) or moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin, St. John's Wort) should be avoided if possible as they may reduce enzalutamide plasma concentration if coadministered. Selection of a concomitant medication with no or minimal CYP3A4 induction potential is recommended.
- Enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Medicinal products with a narrow therapeutic range that are substrates of CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (e.g., phenytoin, warfarin), or CYP2C19, or UGT1A1 (e.g., S-mephenytoin) should be avoided if possible, as enzalutamide may decrease their exposure.
- If enzalutamide coadministration with warfarin cannot be avoided, additional international normalized ratio (INR) monitoring should be conducted.
- Enzalutamide is an inhibitor of human P-glycoprotein (P-gp) and may increase exposure to medicines that are P-gp substrates. Medicinal products with a narrow therapeutic range that are substrates for P-gp (e.g., digoxin, colchicine, dabigatran etexilate) should be used with caution when administered concomitantly with enzalutamide.

Permitted Concomitant Treatment

The following treatments are allowed during the study (and do not require study drug discontinuation) including, but not limited to:

- Blood transfusions and growth factor support per standard of care and institutional guidelines;
- Steroid use (for indication other than prostate cancer) per standard of care;
- Pain therapy per standard of care and institutional guidelines;
- Palliative radiation therapy including external beam radiotherapy or systemic radionuclides (e.g., Samarium or Strontium);
- Vaccine therapy that has prior market authorization and is not intended to treat prostate cancer;
- Palliative surgical procedures to treat skeletal-related events.

Hormonal treatment for treating complications of LHRH analogue treatment (e.g., hot flashes) will be allowed with Medical Monitor approval. In addition, flutamide, bicalutamide or nilutamide are permitted only if given concurrently with LHRH agonist or antagonist to prevent flare (See [Appendix 12.9 Anti-Androgen Usage]).

Duration of Treatment:

Study drug should be continued as long as the subject is tolerating the study drug and until radiographic progression or starting another investigational agent or new therapy for treatment of prostate cancer.

Discontinuation Criteria:

Subject will be discontinued from the study drug treatment if any of the following occur:

- Any adverse event that is intolerable to the subject which cannot be ameliorated by the use of adequate medical intervention and/or dose reduction or that in the opinion of the investigator would lead to undue risk to the subject if dosing is continued.
- Subject who experiences a seizure or any condition that significantly predisposes the subject to seizure such as brain metastasis or clinically evident stroke.
- Subject who experiences a confirmed event of posterior reversible encephalopathy syndrome (PRES) by brain imaging, preferably by MRI.
- Subject initiates another investigational agent or new therapy for prostate cancer.
- Subject who has evidence of radiological disease progression as confirmed and in the judgment

of the investigator is no longer deriving clinical benefit.
- Subject has discontinued ADT (LHRH agonist/antagonist) and has a testosterone value in the noncastrate range (> 50 ng/dL).
- Dose interruptions >14 consecutive days. Dose interruptions for subjects who are deriving clinical benefit from treatment may be extended beyond 14 days after sponsor's approval. Dose interruptions of study drug ≤ 14 days consecutive are permitted at any point during treatment.
- Subject who is, in the opinion of the investigator or the Medical Monitor, noncompliant with the protocol requirements.
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Subject withdraws consent for the study.

Subject will be discontinued from the study follow-up (Safety or Long-term Follow-up) if any of the following occur:

- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Subject withdraws consent for further follow-up.
- Death.
- Study termination by the Sponsor.

Endpoints for Evaluation:

Primary Endpoints

- Time to PSA progression: PSA progression is defined as a ≥ 25% increase and an absolute increase of ≥ 2 µg/L (2 ng/mL) above the nadir (i.e., lowest PSA value observed post baseline or at baseline), which is confirmed by a second consecutive value at least 3 weeks later. (Prostate Cancer Clinical Trials Working Group 3 criteria) (tested by central laboratory)

Secondary Endpoints

- rPFS
- Time to first SSE
- Time to castration resistance
- PSA response (≥ 50%)
- PSA response (≥ 90%)
- Time to initiation of new antineoplastic therapy
- PSA undetectable rate (< 0.2 ng/mL)
- ORR

Exploratory Endpoints

- Time to deterioration of QoL
- Time to pain progression

Safety Endpoints

- Nature, frequency and severity of adverse events
- Safety laboratory tests: biochemistry and hematology
- Physical examination
- ECG
- Vital signs (blood pressure, pulse and temperature)

Statistical Methods:

Sample Size Justification:

The study is planned to randomize approximately 180 subjects (120 subjects in enzalutamide + ADT arm and 60 subjects in placebo + ADT arm, with 10% dropout) in order to observe at least 75 PSA progression events as planned for the final analysis. The sample size calculation is based on the following considerations:

A target hazard ratio (HR) is 0.50. The expected median TTPP for the ADT arm is 9 months as measured from the date of randomization. A target HR of 0.50 corresponds to a 100% increase in median TTPP for the enzalutamide plus ADT arm relative to the placebo plus ADT arm (approximately 18 versus 9 months).

The planned 75 PSA progression events provides approximately 80% power to detect a target HR of 0.50 based on a 2-sided log-rank test and overall significance level of 0.05. This assumed a recruitment period of 15 months and a follow-up period of 12 months.

There are 2 planned analyses, one final analysis at the total planned 75 PSA progression events and one interim analysis at 80% of the total planned events (about 60 PSA progression events providing 61% power to demonstrate superiority at a 2-sided alpha of 0.0244). TTPP will be formally tested at both interim analysis and final analysis at 2-sided 0.0244 and 0.0429 significance level, respectively, for efficacy according to the O'Brien-Fleming boundary as implemented by Lan-DeMets alpha spending function. Data cut-off dates will be set when the planned number of events is reached for the interim and final analyses. If the exact number of events at interim and final analyses are different than planned, the significance level will be adjusted accordingly, based on the O'Brien-Fleming method with a Lan-DeMets alpha spending function. The family-wise type I error rate for this study is strongly controlled at 5% (2-sided) that allows the study to declare positive on primary endpoint TTPP on the ITT population.

Subject Populations:

Intent-to-Treat Population:

The Intent-to-Treat (ITT) population is defined as all subjects who were randomized in this study. The ITT population will be analyzed by treatment arm as randomized (i.e., treatment arm based on randomization assignment). The ITT population will be used to conduct efficacy analyses. For the ORR, only subjects with measurable disease at baseline will be included in the analysis.

Safety Population:

The safety population is defined as all randomized subjects who received at least 1 dose of study drug. The safety population will be analyzed by treatment arm as treated (i.e., based on the treatment the subject actually received rather than the treatment to which the subject was randomized). The safety population will be used to conduct safety analyses.

Efficacy:

Primary Endpoint

- *Time to PSA progression:* PSA progression is defined as a ≥ 25% increase and an absolute increase of ≥ 2 µg/L (2 ng/mL) above the nadir (i.e., lowest PSA value observed post baseline or at baseline), which is confirmed by a second consecutive value at least 3 weeks later. (Prostate Cancer Clinical Trials Working Group 3 criteria) (tested by central laboratory)

Secondary Endpoints

- *rPFS:* Defined as the time from randomization to the first objective evidence of radiographic disease progression as assessed by the investigator or death (defined as death from any cause within 24 weeks from study drug discontinuation), whichever occurs first.
- *Time to first SSE:* Defined as the time from randomization to the occurrence of the first SSE. SSE is defined as radiation or surgery to bone, clinically apparent pathological bone fracture or spinal cord compression.

- *Time to castration resistance:* Defined as the time from randomization to the first castration-resistant event (radiographic disease progression, PSA progression or SSE), whichever occurs first.
- *PSA Response ≥ 50%, PSA Response ≥ 90%*: is defined as ≥ 50% and ≥ 90% reductions in PSA level from baseline to the lowest post-baseline PSA result as determined by the central laboratory, with a consecutive assessment conducted at least 3 weeks later to confirm the PSA response, respectively. The serum PSA response rate will be summarized at each time point. Waterfall plots of the rate of change from baseline will be constructed. PSA response ≥50% and ≥ 90% will be calculated by treatment group for subjects with PSA values at the baseline assessment and at least 1 post-baseline assessment.
- *Time to initiation of a new antineoplastic therapy:* Defined as the time from randomization to the initiation of antineoplastic subsequent to the study treatments.
- *PSA undetectable rate:* Defined as percentage of subjects with detectable (≥ 0.2 ng/mL) PSA at baseline which become undetectable (< 0.2 ng/mL) during study treatment.
- *ORR:* Defined as the percentage of subjects with measurable disease at baseline who achieved a complete or partial response in their soft tissue disease using the RECIST version 1.1 criteria on CT/MRI, and for bone lesions on bone scans.

Exploratory Endpoints

- *Time to deterioration of QoL:* Defined as time from randomization to a 10-point reduction of the FACT-P total score.
- *Time to pain progression:* Defined as time from randomization to an increase of 30% in pain severity score from baseline using the BPI-SF.

Time to event endpoints such as rPFS, time to PSA progression, time to first SSE, time to castration resistance, time to deterioration of QoL, time to pain progression and time to initiation of new antineoplastic therapy will be analyzed using the stratified log-rank test. The stratified Cox Regression analysis, with just treatment effect as a factor in the model, will be used to estimate the HR and the associated 95% CI. The median will be estimated using the Kaplan-Meier method.

The proportion endpoints such as PSA Response ≥ 50%, PSA Response ≥ 90%, PSA undetectable rate and ORR will be analyzed using the stratified Cochran-Mantel-Haenszel score test.

Safety:

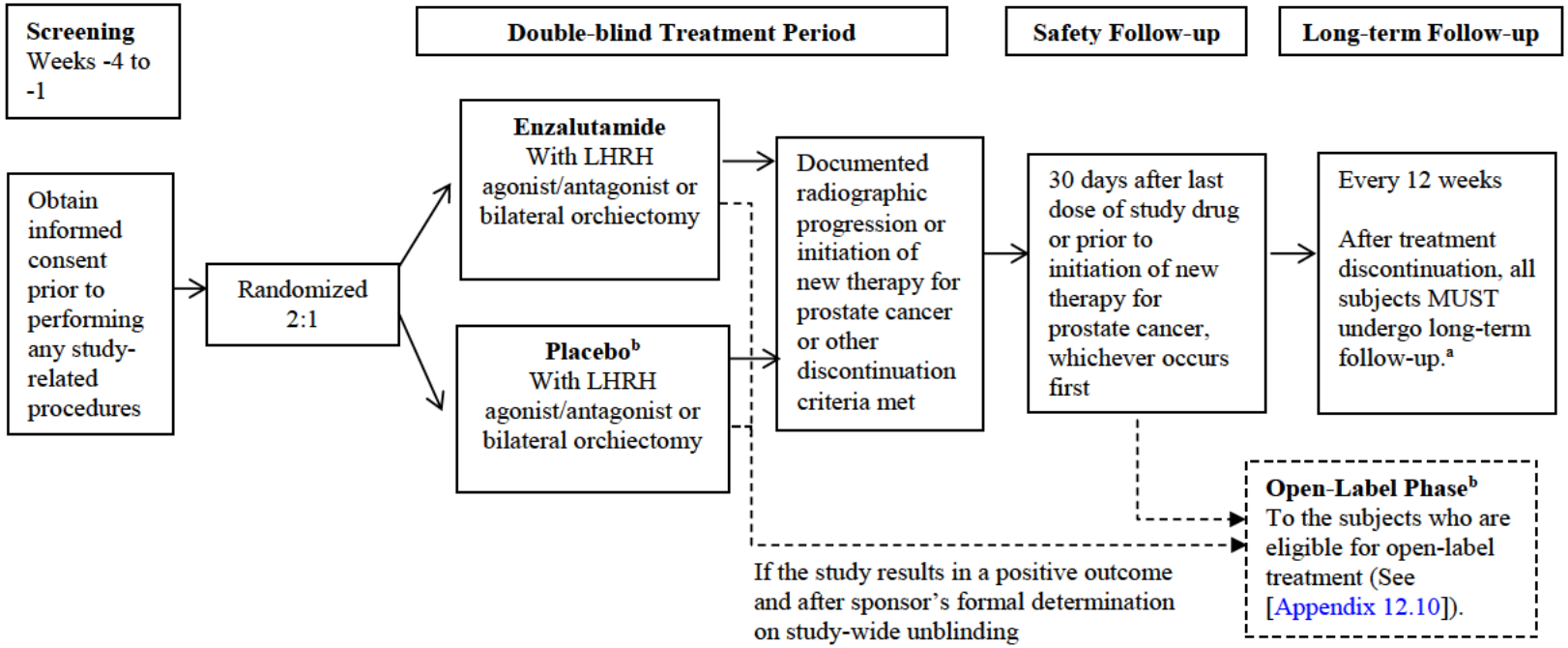
Frequency and severity of adverse events, safety laboratory tests, physical examinations, ECG and vital signs will be summarized descriptively.

Interim Analysis:

An interim analysis is planned to occur after approximately 60 PSA progression events (about 80% of the total planned events) are observed. TTPP will be tested for efficacy according to the O'Brien-Fleming boundary as implemented by Lan-DeMets alpha spending function. Data cut-off dates will be set when the planned number of events is reached for the interim and final analyses. If the exact number of events at interim and final analyses are different than planned, the significance level will be adjusted accordingly, based on the O'Brien-Fleming method with a Lan-DeMets alpha spending function. The IDMC may recommend to the sponsor whether the trial should be terminated or continue unchanged based on interim analysis.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart



LHRH: luteinizing hormone-releasing hormone; PSA: prostate-specific antigen.

a. For those subjects who discontinue study treatment without radiographic disease progression confirmed, radiographic assessments will continue every 12 weeks until confirmed radiographic progression by investigator assessment or the required number of PSA progression events for the final analysis is reached.
b. Before the sponsor's formal determination on study-wide unblinding, open-label enzalutamide will be supplied for free to the subjects in placebo arm who remain on study treatment until confirmed radiographic disease progression and in the judgement of the investigator who is necessary to initiate the next course of therapy till next disease progression based on subject's informed consent. If the study results in a positive outcome and after the sponsor's formal determination on study-wide unblinding via written notice to study sites, open-label enzalutamide will be supplied for free to the subjects in both enzalutamide and placebo arms who remain on study treatment (See [Appendix 12.10] for the flow chart and detailed information).

Table 1 Schedule of Assessments

Study Day	Screening Visit¶¶¶	1#	29	57	85 and Every Subsequent 28 Days	Safety Follow-up	Unscheduled Visit†	Long Term Follow-up‡	
								Post Treatment Follow-up	Survival Follow-up
Study Week	-4 to -1 (28 Days)	1	5	9	13 and Every Subsequent 4 Weeks	30 Days after Last Dose§		Every 12 Weeks	Every 12 Weeks
Window (Days)			± 3	± 3	± 3	± 7	NA	± 7	± 7
Informed Consent	X								
Medical History	X								
Inclusion/Exclusion Criteria	X	X							
Randomization (IRT)		X							
Vital Signs	X	X	X	X	X	X	X		
Physical Examination including Weight¶	X	X	X	X	X	X	X		
Height	X								
12-lead ECG	X	X				X			
Clinical Labs††	X	X	X	X	X	X	X		
PSA‡‡	X	X	X	X	X	X		X	
Testosterone‡‡					X‡‡‡			X	
CT/MRI and Bone Scan§§, ¶¶	X§§				X¶¶,‡‡‡			X	
Chest X-ray or Chest CT/MRI†††	X				X‡‡‡			X	
ECOG Performance Status	X	X	X		X‡‡‡	X	X		
QoL Assessment (QLQ-PR25, EQ-5D-5L, FACT-P, Brief Pain Inventory-Short Form)		X			X‡‡‡	X		X‡	X‡
Adverse Events§§§	X	X	X	X	X	X	X	X§§§	
Previous and Concomitant Medications	X	X	X	X	X	X	X		
Study Drug Dispensing		X	X	X	X				
Study Drug Treatment		X	X	X	X				

CT: computed tomography; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EQ-5D-5L: EuroQol Group-5 Dimension-5 Level Instrument; IRT: Interactive Response Technology; MRI: magnetic resonance imaging; NA: not applicable; PSA: prostate-specific antigen; FACT-P: Functional Assessment of Cancer Therapy-Prostate; QLQ-PR25: Quality of Life Prostate-specific Questionnaire; QoL: quality of life

Before the sponsor's formal determination on study-wide unblinding, open-label enzalutamide will be supplied for free to the subjects in placebo arm who remain on study treatment until confirmed radiographic disease progression and in the judgement of the investigator who is necessary to initiate the next course of therapy till next disease progression based on subject's informed consent. If the study results in a positive outcome and after the sponsor's formal determination on study-wide unblinding via written notice to study sites, open-label enzalutamide will be supplied for free to the subjects in both enzalutamide and placebo arms who remain on study treatment (See [Appendix 12.10]). Subjects who will go to open-label phase will not enter the long-term follow-up.

The alternative approaches which are only permissible in the event of a crisis, is presented in [Section 12.11].

All the assessments on Day 1 need to be performed before treatment.

† Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events at the subject's request or if deemed necessary by the investigator. Procedures and assessments are to be performed as clinically indicated.

‡ After treatment discontinuation, all subjects MUST undergo long-term follow-up. Long-term follow-up assessments will be composed of post-treatment follow-up and survival follow-up. For those subjects who discontinue study treatment without radiographic disease progression confirmed will undergo post-treatment follow-up (calculated from baseline), include monitoring for survival status, disease progression, new antineoplastic therapies for prostate cancer and symptomatic skeletal events. Subjects will continue to be scanned along with collecting PSA and testosterone every 12 weeks until radiographic progression is confirmed by investigator assessment or the required number of PSA progression events for the final analysis is reached. For those subjects who discontinue study treatment due to confirmed radiographic disease progression will undergo survival follow-up (calculated from date of progression), include monitoring for survival status, new antineoplastic therapies for prostate cancer and symptomatic skeletal events, and the follow-up may be conducted by telephone interview. If seen in clinic, QoL assessment will also be completed until the initiation of new antineoplastic therapy for prostate cancer or the required number of PSA progression events for the final analysis is reached. Additional follow-up contacts may be requested.

§ Or prior to initiation of another investigator agent or new antineoplastic therapy for prostate cancer, whichever occurs first.

¶ A brief physical examination is required at each visit, with the exception of the screening visit during which a complete physical examination will be completed.

†† Laboratory assessments include serum chemistries and hematology.

‡‡ For subjects who discontinue study treatment without confirmed radiographic progression, subjects will continue to be collected PSA and testosterone every 12 weeks until radiographic progression is confirmed or the required number of PSA progression events for the final analysis is reached.

§§ The abdominal-pelvic contrast CT scan or MRI, bone scan, chest x-ray or chest contrast CT must occur within 6 weeks of day 1; otherwise the screening visit assessment must be repeated. Radiographic assessments performed prior to informed consent, as part of the routine care, may be used as the baseline assessment if performed within 6 weeks of day 1 and if digital format images are available for submission to the sponsor.

¶¶ The window for all radiological (CT/MRI) assessments is ± 7 days. For subjects who discontinue study treatment without radiographic progression, subjects will continue to be scanned every 12 weeks until radiographic progression is confirmed or the required number of PSA progression events for the final analysis is reached.

††† Chest contrast CT or chest MRI is required at all imaging time points if screening chest x-ray demonstrates metastatic chest disease.

§§§ Adverse events collection begins after the signing of the informed consent for the double-blind period and will be collected until 30 days after the last dose of study drug (including the double-blind period and open-label phase if applicable), or initiation of a new therapy for prostate cancer, or the subject is determined to be a screen failure, whichever occurs first. During the post treatment follow-up period, only symptomatic skeletal events need to be reported.

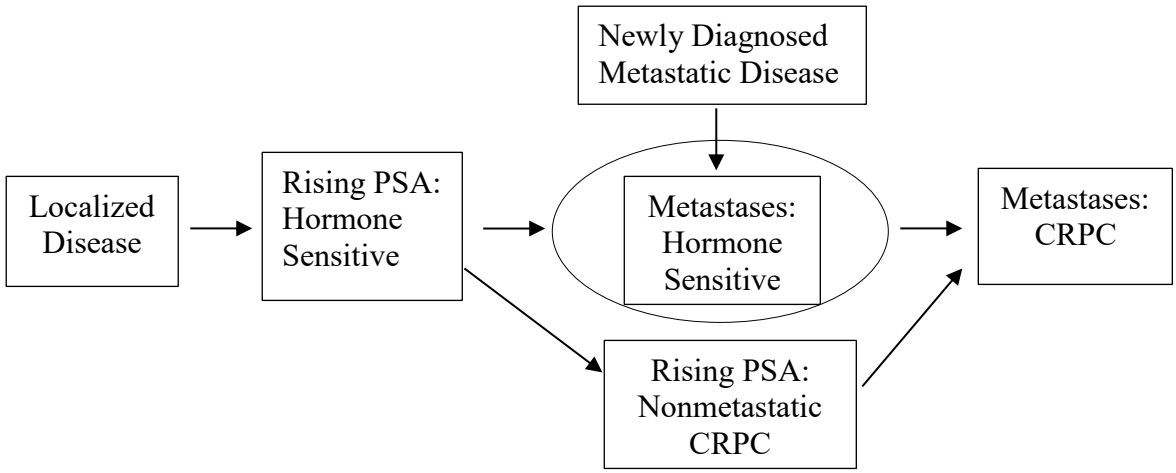
‡‡‡ Testosterone, CT/MRI and Bone Scan, Chest X-ray or Chest CT or MRI, QoL Assessment and ECOG Performance Status will only be performed at day 85 and every subsequent 84 days (13 and every subsequent 12 weeks).

¶¶¶ The Screening period is 28 days. Re-screening may be allowed once and upon discussion with the medical monitor.

1 INTRODUCTION

Worldwide, prostate cancer ranks second in cancer incidence and sixth in cancer mortality in males [Jemal et al, 2011]. Prostate cancer progresses through a series of characteristic clinical states that represent both the natural history of the disease and response to treatment, as indicated in the figure below [Scher & Heller, 2000] [Figure 1]. Prostate cancer progresses from initial diagnosis of either localized or metastatic disease that can then progress with rising PSA levels to metastatic hormone sensitive disease or CRPC, ultimately leading to metastatic CRPC.

Figure 1 Model of Prostate Cancer Progression



CRPC: castration-resistant prostate cancer; PSA: prostate-specific antigen
Source: modified from [Scher and Heller, 2000]

Early in the disease, prostate cancers need relatively high levels of androgens to grow. Such prostate cancers are referred to as androgen dependent or hormone sensitive; therefore, treatments that decrease androgen levels or block androgen activity can inhibit their growth.

Combined androgen deprivation therapy (ADT) with a luteinizing hormone-releasing hormone analogue (LHRHA) or surgical castration, plus a conventional nonsteroidal antiandrogen (NSAA) such as bicalutamide, nilutamide or flutamide, is widely used as initial treatment for hormone sensitive prostate cancer. Meta-analysis of randomized controlled trials showed a 3% absolute improvement in 5-year survival rates with the addition of a conventional NSAA to an LHRHA or surgical castration [Lancet, 2000]. Residual, low-level androgen receptor (AR) signaling, or agonist activity from conventional NSAA, may provide a stimulatory signal to hormone sensitive prostate cancer cells.

1.1 Background

ADT has been the preferred initial treatment for locally advanced and metastatic prostate cancer [Singer et al, 2008]. Presently available androgen deprivation therapies include luteinizing hormone-releasing hormone (LHRH) agonists, LHRH antagonists and antiandrogens. Treatment with LHRH analogues results in prostate-specific antigen (PSA)

decline (the secreted protein product of the AR regulated gene), tumor regression and improved survival, in concert with an increased morbidity and poor quality of life (QoL). LHRH analogue-induced side effects include, but are not limited to, hot flushes, sexual dysfunction, fatigue, reduced cognition, emotional instability/depression, bone loss, insulin resistance, hyperlipidemia, and cardiovascular disease [Keating et al, 2012; Isbarn et al, 2009; Taylor et al, 2009; Tombal & Berges, 2008].

In addition, antiandrogens such as bicalutamide, nilutamide and flutamide are used as standard treatment for hormone sensitive prostate cancer because they block the effect of androgen directly at the AR, although the blockade of the AR is incomplete and partial agonist properties are observed with these agents. According to guidelines, antiandrogen monotherapy should be considered as an alternative to castration in subjects with locally advanced disease. In fact, subjects with an indication for castration therapy may benefit from AR antagonist monotherapy that offers a similar efficacy profile to castration without the reduction in QoL [Makarov & Partin, 2008; Iversen et al, 1998; Kaisary et al, 1995]. It is possible that a more effective and profound AR blockade with a more potent AR blocker like enzalutamide might improve progression-free survival in patients with hormone sensitive prostate cancer.

Also, in a large study (CHAARTED), the use of docetaxel with ADT versus ADT alone was evaluated in subjects with newly diagnosed metastatic hormone sensitive prostate cancer (mHSPC) [Sweeney et al, 2015]. This study enrolled 790 subjects (397 subjects in the ADT plus docetaxel group and 393 subjects in the ADT alone group). ADT plus docetaxel significantly improved median overall survival (OS) (57.6 months) versus ADT alone (44.0 months) (hazard ratio [HR] = 0.61 [95% CI: 0.47, 0.80]; $P < 0.001$). Median time to clinical progression (symptoms or radiographic) was significantly longer in subjects treated with ADT plus docetaxel (33.0 months) versus subjects treated with ADT alone (19.8 months) (HR = 0.61 [95% CI: 0.50, 0.75]; $P < 0.001$).

Consistent with the docetaxel data from CHAARTED, emerging data from the another study (STAMPEDE) also noted that the addition of docetaxel to standard hormonal therapy significantly improved survival among men with newly diagnosed, hormone-naïve, high-risk, locally advanced or metastatic prostate cancer [James et al, 2015; Scher et al, 2015]. In addition, a recent meta-analysis of 3 randomized controlled trials (GETUG-AFU, CHAARTED and STAMPEDE) that evaluated the combination of docetaxel and ADT in hormone sensitive metastatic prostate cancer, demonstrated that in subjects with metastatic prostate cancer the addition of docetaxel was associated with improved OS (HR = 0.74 [95% CI: 0.61, 0.91]; $P = 0.003$) and improvement in progression-free survival (metastatic patients: HR = 0.63 [95% CI: 0.57, 0.70]; $P < 0.001$) [Tucci et al, 2015].

These studies concluded that the combination of standard ADT and 6 cycles of docetaxel resulted in significantly longer OS than that with standard ADT alone in men with hormone sensitive metastatic prostate cancer. The clinical benefit was more pronounced among subjects with a higher burden of disease. Docetaxel treatment was associated with toxicities, but the risk–benefit ratio for its early use in combination with ADT is clearly favorable for use in subjects with high-volume metastatic prostate cancer.

In a phase 3, randomized, double-blind, comparative study of abiraterone acetate plus low-dose prednisone plus ADT versus ADT alone in newly diagnosed patients with high-risk metastatic hormone-naïve prostate cancer (LATITUDE), OS was significantly longer in the abiraterone group than in the ADT alone group (HR = 0.62; 95% CI: 0.51, 0.76; P < 0.001); medians were not reached and 34.7 months, respectively. Radiographic progression-free survival was also significantly longer in patients in the abiraterone group than the ADT alone group (HR = 0.47; 95% CI: 0.39, 0.55; P < 0.001); medians were 33.0 months and 14.8 months, respectively [Fizazi et al, 2017].

Additional therapies for patients with mHSPC are needed because a proportion of these patients treated with current therapies still develop CRPC relatively quickly and suffer from disease-related morbidity and mortality. Study 9785-CL-0335 is ongoing, which will determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT in patients with mHSPC, but doesn't include Chinese population. Study 9785-CL-0336 will have the same study objective but research only in Chinese population, in order to determine whether Chinese population will get clinical benefit.

Enzalutamide is a second generation AR inhibitor that competitively binds the AR with great potency. Additionally, enzalutamide inhibits nuclear translocation of AR, inhibits the association of AR with DNA [Tran et al, 2009], and has no known agonist activity when the AR is overexpressed.

This protocol is based on the hypothesis that earlier use of a therapy shown to be effective in the more advanced state of CRPC will delay progression, emergence of castration-resistant disease. As such, this study aims to determine whether enzalutamide with its superior ability of androgen suppression will improve time to PSA progression of men starting androgen suppression for newly diagnosed metastatic prostate cancer.

1.2 Nonclinical and Clinical Data

1.2.1 Nonclinical Data

The primary pharmacodynamic effect of enzalutamide is inhibition of the AR signaling pathway. Primary pharmacodynamics have been defined in experiments that demonstrated inhibition of AR binding, inhibition of AR nuclear translocation, inhibition of AR chromatin association, inhibition of AR-dependent transcription and cancer cell proliferation, induction of cell death and tumor regression. The nonclinical data on the primary pharmacodynamics of enzalutamide show that it is an AR inhibitor and further, that it is distinct from other antiandrogens in affecting multiple steps in the AR signaling pathway in the setting of AR overexpression. A major human metabolite of enzalutamide, *N*-desmethyl enzalutamide, demonstrated key primary pharmacodynamics with similar potency to the parent molecule.

Enzalutamide and *N*-desmethyl enzalutamide bind to and antagonize the γ-aminobutyric acid (GABA)-gated chloride channel. Enzalutamide given at high doses to mice induced dose-dependent convulsions, an observation that parallels the clinical data showing that dose appears to be an important predictor of the risk of seizure in subjects. As some molecules that antagonize the GABA-gated chloride channel are associated with convulsions, enzalutamide

and *N*-desmethyl enzalutamide may both contribute to the convulsions that were observed in nonclinical studies. Safety pharmacology studies evaluating the central nervous, respiratory and cardiovascular systems did not identify any additional acute effects at exposures relevant to the human clinical dose of 160 mg/day.

Following oral administration in animals, enzalutamide is eliminated slowly from plasma with a long $t_{1/2}$ across species. In vitro studies showed that enzalutamide is metabolized by human recombinant cytochrome P450 (CYP) isoenzymes CYP2C8 and CYP3A4/5. Enzalutamide and/or its major human metabolites caused direct in vitro inhibition of multiple CYP enzymes including CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5. In vitro, enzalutamide caused time-dependent inhibition of CYP1A2. Based on in vitro data, enzalutamide is an inducer of CYP3A4 but is not expected to induce CYP1A2 at therapeutically relevant concentrations.

In vitro data show that enzalutamide and its active metabolite *N*-desmethyl enzalutamide are potential inhibitors, but not substrates, of the efflux transporter P-glycoprotein (P-gp).

Overall, enzalutamide was generally well tolerated in nonclinical species with the most prominent effects occurring in reproductive and hormone sensitive tissues. In studies in rats (4 and 26 weeks) and dogs (4, 13 and 39 weeks), changes in the reproductive organs associated with enzalutamide were decreases in organ weight with atrophy of the prostate and epididymis. Additional changes related to reproductive and hormone sensitive tissues included hypertrophy/hyperplasia of the pituitary gland and atrophy in seminal vesicles in rats and testicular hypospermia, seminiferous tubule degeneration and hypertrophy/hyperplasia of the Leydig cells in dogs. Gender differences were noted in rat mammary glands (i.e., male atrophy and female lobular hyperplasia). Changes in the reproductive organs in both species were consistent with the pharmacological activity of enzalutamide and reversed or partially resolved after an 8-week recovery period. There were no other important changes in clinical pathology or histopathology in any other organ system including the liver in either species.

Hepatocellular toxicity is commonly associated with other antiandrogen compounds such as flutamide and nilutamide and both compounds are associated with liver injury in humans [Brahm et al, 2011; Gomez et al, 1992]. In contrast to other antiandrogens, enzalutamide showed no evidence of hepatotoxicity in animals or in the clinical program.

Electrocardiogram (ECG) and cardiovascular assessments in a toxicity study in dogs showed no treatment-related effects. In vivo and in vitro safety pharmacology studies also demonstrated the absence of cardiovascular enzalutamide related effects.

In a 6-month study in transgenic rasH2 mice, enzalutamide did not show carcinogenic potential (absence of neoplastic findings) at doses up to 20 mg/kg per day (AUC_{24h} ≈317 µg•h/mL), which resulted in plasma exposure levels similar to the clinical exposure (AUC_{24h} 322 •µg·h/mL) in metastatic CRPC patients receiving 160 mg, daily. Daily oral dosing of rats with enzalutamide at 10 to 100 mg/kg for 2 years increased the incidence of neoplastic findings (compared to control) that were considered related to the primary pharmacology of enzalutamide. These included benign thymoma, fibroadenoma in the mammary glands and

benign Leydig cell tumors in the testes in males; benign granulosa cell tumor in the ovaries in females; and adenoma in the pars distalis of the pituitary in both sexes. In addition, urothelial papilloma and carcinoma of urinary bladder in male rats were observed at the 100 mg/kg per day dose and were considered secondary to the irritation caused by the increased urinary crystal/calculi, which is known to occur in rodent species. Leydig cell tumors in rats are generally not considered relevant to humans based on experience with other anti-androgens [Cook et al, 1999]. The human relevance of thymoma, pituitary adenoma and fibroadenoma in rats is unclear, but a potential relevance cannot be ruled out. The exposure levels (based on AUC) achieved in this study for enzalutamide and its metabolites (M1 and M2) in rats were less than or similar to those in prostate cancer patients at the recommended dose of enzalutamide.

Enzalutamide was nonmutagenic in bacteria, nonclastogenic in mammalian cells and nongenotoxic in vivo in mice. The 2 major human metabolites (*N*-desmethyl enzalutamide and an inactive carboxylic acid derivative) were negative for mutagenicity in the bacterial reverse mutation assay (refer to the current Investigator's Brochure).

Enzalutamide could cause fetal harm when administered to a pregnant woman based on its mechanism of action and embryo-fetal toxicity observed in mice. Based on nonclinical findings in repeat-dose toxicology studies, which were consistent with the pharmacological activity of enzalutamide, male fertility may be impaired by treatment with enzalutamide. In studies in mice (4 weeks), rats (4 and 26 weeks) and dogs (4, 13 and 39 weeks), changes in the reproductive organs associated with enzalutamide were decreases in organ weight with atrophy of the prostate and epididymis. In a pharmacokinetic study in pregnant rats with a single oral 30 mg/kg enzalutamide administration on gestation day 14, enzalutamide and/or its metabolites were present in the fetus at a C_{max} that was approximately 0.3 times the concentration found in maternal plasma and occurred 4 hours after administration. Following a single oral administration in lactating rats on postnatal day 14, enzalutamide and/or its metabolites were present in milk at a C_{max} that was 4 times higher than concentrations in the plasma and occurred 4 hours after administration.

1.2.2 Clinical Data

As of 30 August 2019, over 9000 patients with prostate cancer, over 400 women with breast cancer, over 100 patients with HCC and over 300 male subjects with no known cancer (including healthy men and subjects with liver impairment) have received at least 1 dose of enzalutamide in completed and ongoing clinical studies.

The pharmacokinetics and metabolism of enzalutamide have been evaluated in more than 2500 subjects with prostate cancer and in more than 200 healthy male subjects and subjects with mild, moderate, or severe hepatic impairment. Individual daily doses have ranged from 30 to 600 mg.

The pharmacokinetics of a single oral 160 mg dose of enzalutamide were examined in subjects with baseline mild, moderate or severe hepatic impairment (Child-Pugh Class A, B, and C, respectively) and in matched control subjects with normal hepatic function

(Study 9785-CL-0009 and Study 9785-CL-0404). Mild, moderate or severe hepatic impairment did not have a clinically relevant effect on the composite AUC of enzalutamide plus *N*-desmethyl enzalutamide. Therefore, the results indicate that no starting dose adjustment is necessary for subjects with baseline mild, moderate or severe hepatic impairment.

After oral administration to subjects with CRPC, the median time to reach maximum enzalutamide plasma concentrations was 1 hour, and the mean terminal half-life was 5.8 days. Enzalutamide steady state was achieved by day 28, and the accumulation ratio was 8.3-fold. At steady state, enzalutamide showed approximately dose-proportional pharmacokinetics over the range of 30 to 360 mg/day. Steady-state plasma levels of the active metabolite are similar to those of enzalutamide.

A mass balance and biotransformation study in healthy male volunteers showed that enzalutamide is primarily eliminated by hepatic metabolism. A food-effect study showed that food does not have a clinically relevant effect on the AUC of enzalutamide or *N*-desmethyl enzalutamide; therefore, enzalutamide can be taken with or without food.

Based on population pharmacokinetics modeling, age, weight and renal function (creatinine clearance [$CL_{CR} \geq 30$ mL/minute] do not have clinically meaningful effects on enzalutamide exposures; therefore, no dose adjustments are indicated for these covariates. Based on pharmacokinetic data from a study in Japanese subjects with prostate cancer, there were no clinically relevant differences in exposure between Japanese and Caucasian subjects. Clinical data are insufficient to assess the potential effect of severe renal impairment ($CL_{CR} < 30$ mL/minute) and end-stage renal disease on enzalutamide pharmacokinetics.

Drug-drug interaction studies in prostate cancer subjects showed that enzalutamide can affect exposures to certain comedications. At steady state, enzalutamide reduced the AUC of oral midazolam (CYP3A4 substrate), S-warfarin (CYP2C9 substrate) and omeprazole (CYP2C19 substrate) by 86%, 56% and 70%, respectively. Therefore, enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. Substrates of CYP3A4, CYP2C9 and CYP2C19 with a narrow therapeutic index are to be avoided, as enzalutamide may decrease plasma exposure of these drugs. If enzalutamide is coadministered with warfarin (CYP2C9 substrate), additional international normalized ratio (INR) monitoring needs to be conducted. Enzalutamide (160 mg/day) did not have a clinically relevant effect on exposure to intravenous docetaxel (CYP3A4 substrate) or to oral caffeine (CYP1A2 substrate), dextromethorphan (CYP2D6 substrate) or pioglitazone (CYP2C8 substrate).

Drug-drug interaction studies in healthy subjects showed that concomitant medications can affect exposure to enzalutamide. Coadministration of gemfibrozil (a strong CYP2C8 inhibitor) increased the composite AUC of enzalutamide plus *N*-desmethyl enzalutamide by 2.2-fold; therefore, strong CYP2C8 inhibitors are to be avoided. If coadministration with a strong CYP2C8 inhibitor is necessary, the dose of enzalutamide needs to be reduced to 80 mg once daily. Coadministration of itraconazole (strong CYP3A4 inhibitor) increased the composite AUC of enzalutamide plus *N*-desmethyl enzalutamide by 1.3-fold; as this small

change is not clinically meaningful, no dose adjustment is needed when coadministering enzalutamide with CYP3A4 inhibitors. Coadministration of rifampin (strong CYP3A4 and moderate CYP2C8 inducer) decreased the composite AUC of enzalutamide plus *N*-desmethyl enzalutamide by 37%, while C_{max} remained unchanged (Study 9785-CL-0405); as these changes are not considered clinically relevant, no dose adjustment is needed when coadministering enzalutamide with moderate CYP2C8 inducers or CYP3A4 inducers.

The potential for enzalutamide to affect the pharmacokinetics of other drugs via effects on drug transporters was assessed through a series of in vitro experiments. Based on in vitro data, enzalutamide, *N*-desmethyl enzalutamide and/or the carboxylic acid metabolite may be inhibitors of BCRP, MRP2 and OAT3 at clinically relevant systemic concentrations or in the gastrointestinal wall during absorption. Thus, enzalutamide may increase the plasma concentrations of coadministered medicinal products that are BCRP, MRP2 or OAT3 substrates. In vitro experiments also suggest enzalutamide, *N*-desmethyl enzalutamide and the carboxylic acid metabolite do not inhibit OATP1B1, OAT1B3, OCT1, OCT2, OAT1 and OAT3-mediated transport at clinically relevant concentrations. Enzalutamide is not a substrate for OATP1B1, OATP1B3 or OCT1, and *N*-desmethyl enzalutamide is not a substrate for P-gp or BCRP. Based on in vitro data, enzalutamide is an inhibitor but not a substrate for P-gp; however, under conditions of clinical use, enzalutamide may be an inducer of P-gp via activation of pregnane X receptor. Thus, enzalutamide may alter the plasma concentrations of coadministered medicinal products that are P-gp substrates (refer to current Investigator's Brochure).

1.3 Summary of Key Safety Information for Study Drugs

Worldwide, enzalutamide has been approved for the treatment of mCRPC in more than 100 countries/regions; enzalutamide has also been approved for the treatment of patients with nonmetastatic CRPC (nmCRPC) in more than 90 countries/regions (including the US and EU) and patients with mHSPC in more than 85 countries/regions.

The safety profile of enzalutamide is summarized for 5 randomized, placebo-controlled phase 3 studies, comprising 5850 unique patients as follows (hereafter defined as the combined phase 3 studies):

- One study in patients with nmCRPC (PROSPER)
- Two studies in chemotherapy-naïve patients with metastatic CRPC (mCPRC) (PREVAIL and Asian PREVAIL)
- One study in patients with mCRPC previously treated with docetaxel-based chemotherapy (AFFIRM)
- One study of patients with mHSPC (ARCHES)

Several other studies in patients with prostate cancer and healthy volunteers provide additional safety data.

Treatment Exposure

In the double-blind portions of the combined phase 3 studies, the median duration of exposure to enzalutamide was 17.9 months and the median duration of exposure to placebo was 7.1 months. The median TEAE reporting period for the enzalutamide group was over 2-fold longer than for the placebo group, resulting in approximately 10 months of additional safety data collected for patients receiving enzalutamide compared with placebo.

Treatment-emergent Adverse Events

Overall, enzalutamide treatment was generally well tolerated across the combined phase 3 studies. Overall, treatment-emergent adverse events (TEAEs) were experienced by 95.1% of patients in the enzalutamide group and 90.1% of patients in the placebo group of the combined phase 3 studies. When TEAEs occurring in at least 5% of patients in the enzalutamide group and with a ≥ 2% higher incidence than the placebo group were adjusted for treatment duration, the differences between the enzalutamide group and the placebo group were reduced (event rate per 100 patient-years of treatment): hypertension (8.1 enzalutamide vs 5.4 placebo), and fall (8.8 vs 4.7). When adjusted for treatment duration, the other frequently reported TEAEs with a ≥ 2% higher incidence in the enzalutamide group than the placebo group had event rates per 100 patient-years of treatment that were either lower in the enzalutamide group than the placebo group or had an equal event rate: fatigue (21.5 enzalutamide vs 25.3 placebo), back pain (14.6 vs 22.6), nausea (13.8 vs 23.8), arthralgia (13.1 vs 18.9), constipation (11.4 vs 17.6), decreased appetite (11.2 vs 16.0), hot flush (10.9 vs 13.3), diarrhea (10.5 vs 15.2), asthenia (8.8 vs 10.6), headache (6.9 vs 7.0), hematuria (6.7 vs 8.0), musculoskeletal pain (6.6 vs 8.3), edema peripheral (6.4 vs 10.0), weight decreased (6.2 vs 7.3), dizziness (5.9 vs 6.8), nasopharyngitis (4.4 vs 5.7) and insomnia (4.3 vs 5.3).

The pooled phase 3 safety data confirms that convulsion/seizure, cognitive and memory impairment, fatigue related events, neutropenia/neutrophil count decreased, fall, fracture and hypertension are adverse events of special interest (AESI) for enzalutamide. Posterior reversible encephalopathy syndrome (PRES) is also considered an AESI for enzalutamide; however, this is based on cases reported during postapproval use of enzalutamide and not on events occurring in clinical studies.

Severe cutaneous adverse reactions, including acute generalized exanthematous pustulosis, dermatitis bullous, dermatitis exfoliative generalized, drug reaction with eosinophilia and systemic symptoms, erythema multiforme, exfoliative rash, Stevens-Johnson syndrome, toxic epidermal necrolysis and toxic skin eruption have been reported in post-marketing cases.

For more information on the investigational product enzalutamide and on the clinical study experience, refer to the current Investigator's Brochure of enzalutamide.

1.4 Risk-Benefit Assessment

Enzalutamide is a novel small molecule designed to have an increased affinity for the AR and more effective suppression of the androgen pathway in the setting of androgen overexpression [Tran et al, 2009]. Enzalutamide has a higher binding affinity to the AR (8 times greater), has

no agonist activity and has demonstrated superior AR downstream effects in the setting of androgen overexpression compared to bicalutamide in preclinical studies.

The efficacy of enzalutamide in subjects with metastatic prostate cancer who progressed on ADT has been demonstrated in 5 randomized controlled phase 3 studies including study PREVAIL in asymptomatic or mildly symptomatic subjects and AFFIRM in subjects with more advanced disease who previously received docetaxel. Regardless of study arm, subjects remained on ADT in both PREVAIL and AFFIRM studies. These studies demonstrated a statistically significant advantage of enzalutamide treatment over placebo across multiple clinically relevant endpoints such as OS, rPFS, time to first skeletal-related event, time to PSA progression, PSA response rate, best overall soft tissue response, and QoL as measured by the Functional Assessment of Cancer Therapy-Prostate (FACT-P). Study PREVAIL showed a significant benefit of enzalutamide in time to initiation of cytotoxic chemotherapy.

Study PREVAIL (chemotherapy naïve mCRPC subjects) was stopped after a planned interim analysis (conducted when 540 deaths had been reported) and showed a benefit of the active treatment. The rate of rPFS at 12 months was 65% among subjects treated with enzalutamide, as compared with 14% among subjects receiving placebo (81% risk reduction; HR in the enzalutamide group, 0.19; 95% CI, 0.15 to 0.23; $P < 0.001$). A total of 626 subjects (72%) in the enzalutamide group, as compared with 532 subjects (63%) in the placebo group, were alive at the data cutoff date (29% reduction in the risk of death; HR, 0.71; 95% CI, 0.60 to 0.84; $P < 0.0001$). The benefit of enzalutamide was shown with respect to all secondary endpoints, including the time until the initiation of cytotoxic chemotherapy (HR, 0.35), the time until the first skeletal-related event (HR, 0.72), a complete or partial soft tissue response (59% versus 5%), the time until PSA progression (HR, 0.17), and a rate of decline of at least 50% in PSA (78% versus 3%) ($P < 0.001$ for all comparisons).

In PREVAIL, at 5 years a statistically significant increase in OS time was observed in patients treated with enzalutamide compared to placebo (HR = 0.835, 95% CI: 0.751, 0.928; P = 0.0008; median: 35.5 and 31.4 months, respectively). The 5-year OS rate was 26% for the enzalutamide arm compared to 21% for the placebo arm, despite that 28% of patients on placebo crossed over to enzalutamide and there was a high rate of subsequent antineoplastic therapy use for prostate cancer. The significant treatment effect seen in earlier analyses was maintained.

Study AFFIRM (postchemotherapy mCRPC subjects) demonstrated that enzalutamide treatment decreased the risk of death by 37% (HR, 0.631 [0.529, 0.752]; $P < 0.0001$) compared with placebo treatment. The median survival was 18.4 months in the enzalutamide arm and 13.6 months in the placebo arm (difference = 4.8 months). The statistically significant and clinically meaningful benefit of enzalutamide treatment as measured by OS was seen in all prespecified subject subgroups and observed despite 42.0% of enzalutamide-treated and 61.4% of placebo-treated subjects receiving subsequent therapies to treat prostate cancer, including abiraterone (20.9% versus 24.3%) and cabazitaxel (9.8% versus 13.8%), both shown to improve OS following docetaxel treatment. Enzalutamide

treatment also resulted in significant improvements over placebo treatment in all key secondary efficacy endpoints.

In a phase 3, randomized, placebo-controlled study (PROSPER) in patients with nonmetastatic CRPC at high risk of disease progression, treatment with enzalutamide has demonstrated a consistent and clinically meaningful improvement in the primary metastasis-free survival (MFS) endpoint, as well as a delay in the time to onset of new antineoplastic therapies, including cytotoxic chemotherapy. The final analysis of OS (based on a data cutoff date of 15 Oct 2019) showed a statistically significant and clinically meaningful improvement in survival favoring enzalutamide and a 26.6% reduction in the risk of death (HR = 0.734, 95% CI: 0.608, 0.885; P = 0.0011). The efficacy observed with enzalutamide in PROSPER represents a clinically meaningful benefit to patients with nonmetastatic CRPC. Overall, enzalutamide has consistently and robustly demonstrated substantial clinical benefits to patients across the CRPC disease continuum.

In addition, in a phase 2, open-label, single-arm study (9785-CL-0321) in patients with hormone-naïve prostate cancer, 92.5% (62 of 67) of patients had a ≥ 80% decline in PSA from baseline at week 25. Of the 54 patients who were on treatment for 1 year (week 49), 100% had a ≥ 80% decline in PSA from baseline. Of the 26 evaluable patients with metastatic disease at study entry, the best overall response by 2 years (week 97) was 13 (50.0%) patients with CR, 4 (15.4%) patients with PR, 3 (11.5%) patients with non-CR/non-progressive disease (PD), 2 (7.7%) patients with stable disease, 3 (11.5%) patients with PD and 1 (3.8%) patient was not evaluated. At week 97 (2 years of treatment), 45 of 67 (67.2%) patients had a PSA response ≥ 80%; All 45 (100%) patients who were on treatment for 2 years had a ≥ 80% decline in PSA from baseline.

Lastly, the primary efficacy analysis in ARCHES demonstrated a statistically significant, robust and substantial improvement in radiographic progression-free survival together with clinically meaningful improvements in the key secondary endpoints of time to PSA progression, time to start of a new antineoplastic therapy, PSA undetectable rate and objective response rate and a trend in OS (observed at the time of interim analysis) in favor of enzalutamide plus ADT versus placebo plus ADT treatment. For the secondary endpoints, the ARCHES study demonstrated that enzalutamide prolonged the time to the first symptomatic skeletal event and time to castration-resistance. Assessments of patient-reported outcomes data showed that patients receiving enzalutamide plus ADT in ARCHES had a high baseline level of quality of life, which was maintained over time.

Based on the safety information collected to date in clinical trials and in commercial use, the safety profile experienced by patients remains consistent with the approved product label as well as events that can be seen in patients with prostate cancer. The safety profile in mHSPC patients in this study is expected to be consistent with the established safety profile for enzalutamide. To date, the important identified risks associated with enzalutamide are ischemic heart disease, fall, fracture and seizure.

While serious adverse events (SAEs) such as seizure have occurred in patients receiving treatment with enzalutamide, these events have been rare. To mitigate the risk of seizure, subjects with a history of seizure or any condition that may predispose to seizure (e.g., prior cortical stroke or significant brain trauma, brain arteriovenous malformation) are excluded from the trial. Study drug discontinuation is required for subjects experiencing either seizure or PRES. In addition to these patient exclusion and discontinuation requirements, the study design includes safety labs, scans and guidance related to concomitant medications to minimize the risks associated with enzalutamide and ensure timely intervention if needed.

Based on the information known about the drug and the efficacy results that have been consistently demonstrated in both PREVAIL and AFFIRM, the risk-benefit assessment supports the investigation of enzalutamide plus ADT in men with mHSPC who are hormone sensitive. Medical monitor will be responsible for reviewing the unblinded data from the trial to ensure the safety of the subjects.

The totality of the efficacy and safety data demonstrate a favorable benefit-risk balance for the use of enzalutamide in men with mCRPC and for the continued investigation of enzalutamide in men with earlier stage prostate cancer.

2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

2.1 Study Objectives

The objective of this phase 3 study is to evaluate the efficacy and safety of enzalutamide plus ADT versus placebo plus ADT in Chinese subjects with mHSPC.

2.1.1 Primary Objective

- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by time to prostate-specific antigen (PSA) progression based on central laboratory test

2.1.2 Secondary Objectives

- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by radiographic progression-free survival (rPFS)
- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by time to first Symptomatic Skeletal Event (SSE)
- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by time to castration resistance
- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by PSA response (≥ 50%)
- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by PSA response (≥ 90%)

- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by time to start of new antineoplastic therapy
- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by PSA undetectable rate (< 0.2 ng/mL)
- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by objective response rate (ORR)

2.1.3 Exploratory Objectives

- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by QoL (as measured by Quality of Life Prostate-specific Questionnaire [QLQ-PR25] / FACT-P and EuroQol Group-5 Dimension-5 Level Instrument [EQ-5D-5L])
- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by worsening of pain (as measured by Brief Pain Inventory-Short Form [BPI-SF])

2.1.4 Safety Objective

- To determine the safety of enzalutamide plus ADT as compared to placebo plus ADT

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This is a multicenter phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of enzalutamide plus ADT versus placebo plus ADT in Chinese subjects with mHSPC.

Approximately 180 Chinese subjects will be randomized centrally enzalutamide plus ADT or placebo plus ADT (2:1), and the randomization will be stratified by volume of disease (low versus high) and prior docetaxel therapy for prostate cancer (no prior docetaxel, prior docetaxel). High volume of disease is defined as metastases involving the viscera or, in the absence of visceral lesions, there must be 4 or more bone lesions, at least 1 of which must be in a bony structure beyond the vertebral column and pelvic bone. Prior docetaxel therapy is defined as 1 or more cycles of docetaxel but no more than 6 cycles. Re-screening may be allowed once after screening failure upon discussion with the medical monitor.

Study drug therapy should be continued as long as the subject is tolerating the study drug and continues ADT until radiographic disease progression is documented as outlined in [Section 5.3.1.2 Computed Tomography (CT)/Magnetic Resonance Imaging (MRI) and Bone Scan] or starting another investigational agent or new therapy for treatment of prostate cancer. It is recommended that subjects remain on study treatment until confirmed radiographic disease progression. Subjects who discontinue study treatment without confirmed radiographic disease progression will continue to follow the PSA and radiographic assessment schedule until confirmed radiographic disease progression event or the required number of PSA progression events for the final analysis is reached. In the judgment of the Investigator, for subjects who discontinue study treatment with confirmed PSA progression by central

review, blinding should be maintained until confirmed radiographic disease progression. In consultation with the medical monitor, unblinding of the study treatment assignment may be performed after radiographic progression if the subject discontinues from the study treatment and in the judgement of the investigator this information is necessary to determine the next course of therapy. An Independent Data Monitoring Committee (IDMC) will assess the efficacy data at a planned interim analysis which will occur after at least 60 events (about 80% of the total planned events), and safety data will also be considered at the same time when IDMC makes recommendations based on the efficacy data from the benefit-risk perspective.

Before the sponsor's formal determination on study-wide unblinding, open-label enzalutamide will be supplied for free to the subjects in placebo arm who remain on study treatment until confirmed radiographic disease progression and in the judgement of the investigator who is necessary to initiate the next course of therapy till next disease progression based on the subject's informed consent. If the study results in a positive outcome and after the sponsor's formal determination on study-wide unblinding via written notice to study sites, open-label enzalutamide will be supplied for free to the subjects in both enzalutamide and placebo arms who remain on study treatment.

Study films (CT/MRI and bone scan) should be read on site and also be submitted in digital format to the sponsor-designated facility in case independent central review is required after the end of study. Each site should ideally designate the same reader who will evaluate the images for any one subject for the duration of the trial.

Radiographic disease progression is defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 for soft tissue disease or the appearance of 2 or more new lesions on bone scan. The documentation and confirmation required for the determination of radiographic progression is listed in [Section 5.3.1.2 CT/MRI and Bone Scan].

The following assessments of prostate cancer status will be collected during the course of the study: PSA, soft tissue disease on CT scan or on MRI, bone disease on radionuclide bone scans, survival status, EQ-5D-5L, QLQ-PR25, FACT-P for QoL and BPI-SF for pain symptom assessment.

Throughout the study, safety and tolerability will be assessed by the recording of AEs, vital signs, physical examinations, 12-lead ECGs, and safety laboratory evaluations.

Subjects will have a safety follow-up visit 30 days after their last dose of study drug or prior to initiation of new antineoplastic therapy for prostate cancer, whichever occurs first.

The sponsor will monitor study enrollment for proportion of subjects enrolled with a history of prior docetaxel treatment, and may either change the sample size, or cap the number of subjects who received prior docetaxel to ensure that the primary endpoint is not driven either by the subjects who received prior docetaxel, or by the subjects who did not receive prior docetaxel.

The alternative approaches which are only permissible in the event of a crisis, is presented in [Section 12.11].

2.2.2 Dose Rationale

Enzalutamide 160 mg administered orally, once daily, is the daily dose recommended by regulatory agencies in countries where enzalutamide is approved.

2.3 Endpoints

2.3.1 Primary Endpoints

Time to PSA progression: PSA progression is defined as a ≥ 25% increase and an absolute increase of ≥ 2 µg/L (2 ng/mL) above the nadir (i.e., lowest PSA value observed post baseline or at baseline), which is confirmed by a second consecutive value at least 3 weeks later. (Prostate Cancer Clinical Trials Working Group 3 criteria) (tested by central laboratory)

2.3.2 Secondary Endpoints

- rPFS
- Time to first SSE
- Time to castration resistance
- PSA response (≥ 50%)
- PSA response (≥ 90%)
- Time to initiation of new antineoplastic therapy
- PSA undetectable rate (< 0.2 ng/mL)
- ORR

2.3.3 Exploratory Endpoints

- Time to deterioration of QoL
- Time to pain progression

2.3.4 Safety Endpoints

- Nature, frequency and severity of AEs
- Safety laboratory tests: biochemistry and hematology
- Physical examination
- ECG
- Vital signs (blood pressure, pulse and temperature)

3 STUDY POPULATION

3.1 Selection of Study Population

The study population will include approximately 180 Chinese men with metastatic hormone sensitive prostate cancer.

3.2 Inclusion Criteria

Subject is eligible for the study if all of the following apply:

1. Institutional Review Board (IRB)-/Independent Ethics Committee (IEC)-approved written informed consent and privacy language as per national regulations must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is considered an adult according to local regulation at the time of signing informed consent.
3. Subject is diagnosed with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, signet cell or small cell histology.
4. Subject has metastatic prostate cancer documented by positive bone scan (for bone disease) or measurable metastatic lesions on CT or MRI scan (for soft tissue). Subjects whose disease spread is limited to regional pelvic lymph nodes are not eligible.
5. Once randomized at day 1, subject must maintain ADT with an LHRH agonist or antagonist during study treatment or have a history of bilateral orchiectomy (i.e., medical or surgical castration).
6. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at screening.
7. Subject has an estimated life expectancy of ≥ 12 months as assessed by the investigator.
8. Subject is able to swallow the study drug and comply with study requirements.
9. A sexually active male subject with female partner(s) who is of childbearing potential is eligible if:
    - Agrees to use a male condom starting at screening and continue throughout the study treatment and for at least 3 months after the last dose of study drug. If the male subject has not had a vasectomy or is not sterile at least 6 months prior to screening as defined below his female partner(s) is utilizing 1 form of highly effective birth control* per locally accepted standards starting at screening and continue throughout study treatment and for at least 3 months after the male subject receives his last dose of study drug.

*Highly effective forms of birth control include:

- Consistent and correct usage of established hormonal contraceptives that inhibit ovulation
- Established intrauterine device (IUD) or intrauterine hormone releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomy (A vasectomy is a highly effective contraception method provided the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used)
- Male is sterile due to a bilateral orchiectomy or radical cystoprostatectomy/removal of seminal vesicles
- Sexual Abstinence is considered a highly effective method only if defined as refraining from heterosexual activity during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant

10. Subject must agree to abstinence or use a condom throughout the study period and for at least 3 months after the last dose of study drug if engaging in sexual intercourse with a pregnant or breastfeeding partner(s).
11. Subject must agree not to donate sperm from first dose of study drug through 3 months after the last dose of study drug.
12. Subject agrees not to participate in another interventional study while on treatment.

Waivers to the inclusion criteria will **NOT** be allowed.

3.3 Exclusion Criteria

Subject will be excluded from participation if any of the following apply:

1. Subject has received any prior pharmacotherapy, radiation therapy or surgery for metastatic prostate cancer (the following exceptions are permitted):
    - Up to 3 months of ADT with LHRH agonists or antagonists or orchiectomy with or without concurrent antiandrogens prior to day 1, with no radiographic evidence of disease progression or rising PSA levels prior to day 1;
    - Subject may have 1 course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease if it was administered at least 4 weeks prior to day 1;
    - Up to 6 cycles of docetaxel therapy with final treatment administration completed within 2 months of day 1 and no evidence of disease progression during or after the completion of docetaxel therapy;
    - Up to 6 months of ADT with LHRH agonists or antagonists or orchiectomy with or without concurrent antiandrogens prior to day 1 if subject was treated with docetaxel, with no radiographic evidence of disease progression or rising PSA levels prior to day 1;

- Prior ADT given for < 39 months in duration and > 9 months before randomization as neoadjuvant/adjuvant therapy.

2. Subject had a major surgery within 4 weeks prior to day 1.
3. Subject received treatment with 5-α reductase inhibitors (finasteride, dutasteride) within 4 weeks prior to day 1.
4. Subject received treatment with estrogens, cyproterone acetate or androgens within 4 weeks prior to day 1.
5. Subject received treatment with systemic glucocorticoids greater than the equivalent of 10 mg per day of prednisone within 4 weeks prior to day 1, intended for the treatment of prostate cancer.
6. Subject received treatment with herbal medications that have known hormonal antiprostate cancer activity and/or are known to decrease PSA levels within 4 weeks prior to day 1.
7. Subject received prior aminoglutethimide, ketoconazole, abiraterone acetate or enzalutamide for the treatment of prostate cancer or participation in a clinical study of an investigational agent that inhibits the AR or androgen synthesis (e.g., TAK-700, ARN-509, ODM-201).
8. Subject received investigational agent within 4 weeks prior to day 1.
9. Subject has known or suspected brain metastasis or active leptomeningeal disease.
10. Subject has a history of another invasive cancer within 3 years of screening, with the exception of fully treated cancers with a remote probability of recurrence based on investigator assessment.
11. Subject has absolute neutrophil count < 1500/μL, platelet count < 100000/μL or hemoglobin < 10 g/dL (6.2 mmol/L) at screening. NOTE: May not have received any growth factors within 7 days or blood transfusions within 28 days prior to the hematology values obtained at screening.
12. Subject has total bilirubin (TBL) ≥ 1.5 × the upper limit of normal (ULN) (except subjects with documented Gilbert's disease), or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2.5 × the ULN at screening.
13. Subject has creatinine > 2 mg/dL (177 μmol/L) at screening.
14. Subject has albumin < 3.0 g/dL (30 g/L) at screening.
15. Subject has a history of seizure or any condition that may predispose to seizure (e.g., prior cortical stroke or significant brain trauma, brain arteriovenous malformation).
16. Subject has history of loss of consciousness or transient ischemic attack within 12 months prior to day 1.
17. Subject has clinically significant cardiovascular disease, including the following:

- Myocardial infarction within 6 months prior to screening;
- Unstable angina within 3 months prior to screening;
- New York Heart Association class III or IV congestive heart failure or a history of New York Heart Association class III or IV congestive heart failure unless a screening echocardiogram or multigated acquisition scan performed within 3 months before the randomization date demonstrates a left ventricular ejection fraction ≥ 45%;
- History of clinically significant ventricular arrhythmias (e.g., sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes);
- History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place;
- Hypotension as indicated by systolic blood pressure < 86 mm Hg at screening;
- Bradycardia as indicated by a heart rate of ≤ 45 beats per minute on the screening ECG;
- Uncontrolled hypertension as indicated by a minimum of 2 consecutive blood pressure measurements showing systolic blood pressure > 170 mm Hg or diastolic blood pressure > 105 mm Hg at screening.

18. Subject has gastrointestinal disorder affecting absorption.
19. Subject has any concurrent disease, infection or comorbid condition that interferes with the ability of the subject to participate in the study, which places the subject at undue risk or complicates the interpretation of data in the opinion of the investigator.
20. Subject received bisphosphonates or denosumab within 2 weeks prior to day 1 unless administered at stable dose or to treat diagnosed osteoporosis.
21. Subject has shown a hypersensitivity reaction to the active pharmaceutical ingredient or any of the study capsule components, including Labrasol®, butylated hydroxyanisole (BHA), and butylated hydroxytoluene (BHT).

Waivers to the exclusion criteria will NOT be allowed.

4 TREATMENT(S)

4.1 Identification of Investigational Product(s)

4.1.1 Study Drug(s)

Enzalutamide (formerly MDV3100) will be supplied to sites as 40 mg white to off-white oblong capsules. The oral soft gelatin capsules are filled with a clear, yellowish solution that contains the 2 antioxidants, BHA and BHT, and enzalutamide active ingredient (40 mg), all dissolved in the nonionic surfactant, Labrasol (caprylocaproyl polyoxylglycerides).

The clinical material is packaged in high-density polyethylene (HDPE) bottles with child-resistant closures. The capsules should be stored in the original bottle in a secure location with limited access at 20°C to 25°C; excursions from 15°C to 30°C are permitted.

4.1.2 Comparative Drug(s)

The placebo for enzalutamide will be supplied as oral soft gelatin capsules that consist of Labrasol and the same relative concentration of the 2 preservatives, BHA and BHT, that are also present in the active drug.

The clinical material is packaged in HDPE bottles with child-resistant closures. The capsules should be stored in the original bottle in a secure location with limited access at 20°C to 25°C; excursions from 15°C to 30°C are permitted.

4.2 Packaging and Labeling

All medication used in this study will be prepared, packaged, and labeled under the responsibility of qualified staff at Astellas Pharma Global Development, Inc (APGD)- sponsor's designee in accordance with APGD or sponsor's designee standard operating procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable local laws/regulations.

Each bottle will bear a label conforming to regulatory guidelines, GMP and local laws and regulations, which identifies the contents as investigational drug.

The study centers will be provided bottles containing 124 capsules of enzalutamide 40 mg capsules and bottles containing 124 capsules of matching placebo.

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 study drug is handled and stored according to labeled storage conditions;
- that study drug with appropriate expiry/retest only is dispensed to study subjects in accordance with the protocol;
- that any unused study drug is returned to the sponsor, unless prior approval is received from the sponsor allowing local standard procedures for the alternative disposition of unused study drug.

Drug inventory and accountability records for the study drugs 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 or designee agrees not to supply study drugs to any persons except the eligible subjects in this study in accordance with the protocol.

- The investigator or designee will store and take accountability of the study drugs in conforming to the procedures for handling the study drugs as written by the sponsor.
- The investigator or designee will prepare and retain records of the study drug's receipt, the inventory at the study site, the use by each subject, and the return to the sponsor or alternative disposal of unused study drugs if approved by the sponsor. These records should include dates, quantities, batch/serial numbers, expiration dates, and the unique code numbers assigned to the study drugs and subjects.
- 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 for this responsibility.

4.4 Blinding

4.4.1 Blinding Method

This is a double-blind study. Subjects will be randomized to receive enzalutamide or placebo in a double-blind fashion such that neither the investigator, sponsor's study management team, clinical staff, nor the subject will know which agent is being administered. The randomization number will be assigned based on information obtained from the Interactive Response Technology (IRT).

4.4.2 Confirmation of the Indistinguishability of the Study Drugs

For the purpose of this study, the efficacy and safety of enzalutamide and placebo will be compared in a double-blind manner. Enzalutamide 40 mg capsule and placebo will be indistinguishable from one another in appearance, and packaging for each treatment group will also be indistinguishable from one another in appearance.

4.4.3 Retention of the Assignment Schedule and Procedures for Treatment Code Breaking

The randomization list and study medication blind will be maintained by the IRT system.

Unblinding of the study treatment assignment may be performed if the subject discontinues from the study treatment with confirmed radiographic disease progression and in the judgement of the investigator this information is necessary to determine the next course of therapy. Prior to unblinding in this scenario, the investigator must contact the Astellas Medical Monitor.

4.4.4 Breaking the Treatment Code for Emergency

The treatment code for each randomized subject will be provided by the IRT in the event of a medical emergency requiring knowledge of the treatment assigned to the subject. If possible, the Astellas Medical Monitor should be contacted prior to unblinding. The time, date, subject number and reason for obtaining any of these codes, and therefore breaking the blind, must be

documented in the study file. They must only be requested by the investigator or other persons designated as subinvestigators. No subjects or other study personnel will be made aware of the treatment given to any subject unless a medical emergency necessitates such disclosure.

Any unblinding by the investigational staff must be reported immediately to the sponsor and must include an explanation of why the study medication was unblinded.

4.4.5 Breaking the Treatment Code by the Sponsor

The sponsor may break the treatment code for subjects who experience a suspected unexpected serious adverse reaction (SUSAR), in order to determine if the individual case or a group of cases requires expedited regulatory reporting. Individual Emergency Codes will be provided to the limited staff that is responsible to break the codes for all SUSAR cases for reporting purposes.

4.5 Assignment and Allocation

Subjects will be entered into the IRT system at screening and assigned a subject number. Randomization will be performed via the IRT system and treatment assigned in a 2:1 ratio to enzalutamide 160 mg/day or placebo. Prior to the initiation of the study treatment, on day 1, the site staff will contact the IRT system in order to determine the randomly assigned treatment. Subjects will be stratified by prior docetaxel (yes, no) and disease volume (low versus high). High-volume disease is defined as metastases involving the viscera or, in the absence of visceral lesions, there must be 4 or more bone lesions, at least 1 of which must be in a bony structure beyond the vertebral column and pelvic bone. Specific procedures for randomization through the IRT system are contained in the study procedures manual.

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

Study drug consists of enzalutamide provided as 40 mg capsules to be taken as 160 mg (4 capsules) orally once daily or matching placebo. Study drug is to be taken until disease progression, unacceptable toxicity or any other discontinuation criteria are met.

Study drug will be self-administered at home by the subject and taken as close to the same time each day as possible. Study drug can be taken with or without food. Subjects should not make up missed or vomited doses; dosing should resume the following day unless otherwise instructed.

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

During the study, subjects who experience a National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) guidelines (version 4.03) grade 3 or higher AE (except liver function test [LFT] AE) toxicity that is attributed to the study drug and cannot be ameliorated by the use of adequate medical intervention and/or dose reduction may interrupt

study drug treatment for 1 week or until the toxicity grade improves to grade 2 or lower in severity. Study drug may be restarted at the original dose (160 mg/day) or a reduced dose (120 mg or 80 mg/day). If restarted at a lower dose or if interrupted for > 2 weeks, the Medical Monitor must be consulted. After dose reduction, based on subject tolerance, study drug may be increased to a maximum dose of 160 mg/day per investigator discretion.

Enzalutamide must be interrupted during the evaluation of symptoms suspicious of PRES (headache, lethargy, confusion, blindness and other visual and neurological disturbances, with or without associated hypertension).

5.1.3 Previous and Concomitant Treatment (Medication and Nonmedication Therapy)

Medications taken within 28 days prior to the screening visit and up to the first dose of study medication will be documented on the appropriate case report form (CRF) as a prior medication.

Medications taken after the first dose of study medication up until the final follow-up visit will be documented on the appropriate CRF as concomitant medication.

Prior and concomitant medications include all vitamins, herbal remedies, over the counter, and prescription medications.

5.1.3.1 Required Concomitant Treatment

All subjects are required to receive background therapy with ADT, either bilateral orchiectomy or an LHRH agonist or antagonist, which must be maintained during study treatment, as per standard of care (SOC).

An LHRH agonist or antagonist will be provided from the site's stock and administered in accordance with prescribing information.

5.1.3.2 Prohibited Concomitant Treatment

A list of excluded concomitant medications is provided in [Appendix 12.4 List of Excluded Concomitant Medications]. The following medications are prohibited within 4 weeks of day 1 and during the study treatment period:

- 5 α-reductase inhibitors (finasteride, dutasteride);
- Estrogens;
- Cyproterone acetate, megestrol acetate;
- Biologic or other agents with antitumor activity against prostate cancer (with the exception of those therapies identified in exclusion criterion No. 1);
- Systemic glucocorticoids greater than the equivalent of 10 mg per day of prednisone intended for the treatment of prostate cancer;
- Herbal medications that have known hormonal antiprostate cancer activity and/or are known to decrease PSA levels (i.e., saw palmetto);

- Androgens (testosterone, dihydroepiandrosterone, etc.);
- Investigational agents.

In addition, bisphosphonates and denosumab are prohibited unless stabilized for 2 weeks prior to randomization and held constant, as tolerated, throughout study treatment or administered for diagnosis of osteoporosis.

5.1.3.3 Enzalutamide Drug Interaction

There is a potential for enzalutamide to affect exposures to other medicinal products, or for other medicinal products to affect exposure to enzalutamide:

- Strong CYP2C8 inhibitors (e.g., gemfibrozil) are to be avoided. If subject must be coadministered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily. If coadministration of the strong inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.
- Strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin) or moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin, St. John's Wort) should be avoided if possible as they may reduce enzalutamide plasma concentration if coadministered. Selection of a concomitant medication with no or minimal CYP3A4 induction potential is recommended.
- Enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Medicinal products with a narrow therapeutic range that are substrates of CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (e.g., phenytoin, warfarin), or CYP2C19, or UGT1A1 (e.g., S-mephenytoin) should be avoided if possible, as enzalutamide may decrease their exposure.
- If enzalutamide coadministration with warfarin cannot be avoided, additional international normalized ratio (INR) monitoring should be conducted.
- Enzalutamide is an inhibitor of human P-glycoprotein (P-gp) and may increase exposure to medicines that are P-gp substrates. Medicinal products with a narrow therapeutic range that are substrates for P-gp (e.g., digoxin, colchicine, dabigatran etexilate) should be used with caution when administered concomitantly with enzalutamide.

5.1.3.4 Permitted Concomitant Treatment

The following treatments are allowed during the study (and do not require study drug discontinuation) including, but not limited to:

- Blood transfusions and growth factor support per SOC and institutional guidelines;
- Steroid use (for indication other than prostate cancer) per SOC;
- Pain therapy per SOC and institutional guidelines;

- Palliative radiation therapy including external beam radiotherapy or systemic radionuclides (e.g., Samarium or Strontium);
- Vaccine therapy that has prior market authorization and is not intended to treat prostate cancer;
- Palliative surgical procedures to treat skeletal-related events.

Hormonal treatment for treating complications of LHRH analogue treatment (e.g., hot flashes) will be allowed with Medical Monitor approval. In addition, flutamide, bicalutamide or nilutamide are permitted if given concurrently with LHRH agonist or antagonist to prevent flare (See [Appendix 12.9 Anti-Androgen Usage]).

5.1.4 Treatment Compliance

Study subjects should be counseled on the need to meet 100% compliance with study drug unless study drug is withheld for a toxicity. Investigator or designee should ensure that study subjects meet this goal throughout the study period. Compliance will be verified by the accounting of study drug. When study drug is administered at the research facility, it will be administered under the supervision of study personnel. If compliance per visit is less than 80% or higher than 120% of the planned dosage, and study drug was not withheld and there were no study drug reductions, the investigator or designee is to counsel the subject on the importance of taking the study drug.

Compliance of the study drug will be monitored by the accounting of unused medication returned by the subject at visits. Compliance will be documented.

5.1.5 Criteria for Continuation of Treatment

Not applicable.

5.1.6 Restriction During the Study

Not applicable.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

Demographic information will be collected at the screening visit for all subjects and will include age or date of birth, gender, race and ethnicity (as local regulations allow).

5.2.2 Medical History

Medical history will be collected at the screening visit for all subjects and includes all significant medical conditions that have occurred or are currently ongoing at time of consent. The condition, onset date and recovery date will be collected. NCI-CTCAE (version 4.03) grade will be collected for conditions that are ongoing at time of consent. Cancer risk factor information will also be collected.

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

Prostate cancer history will be collected at the screening visit and will include histological or cytological diagnosis, date of diagnosis, Gleason score and associated treatment. Date of diagnosis of metastatic disease, location of metastatic disease lesions, and all previous and/or ongoing treatment will also be documented during screening visit.

5.3 Efficacy Assessment

5.3.1 Efficacy Assessment

5.3.1.1 PSA

Blood samples for PSA will be collected at each scheduled visit during study treatment and at the safety follow-up visit. All samples will be analyzed by sponsor designated central laboratory.

5.3.1.2 CT/MRI and Bone Scan

Radiographic imaging will be performed using CT or MRI and bone scan.

Radiographic assessments performed prior to informed consent, as part of routine care, may be used as the baseline assessment if performed within 6 weeks of day 1 and if digital format images are available for submission to the sponsor.

Following baseline imaging, subsequent scans including abdominal-pelvic CT, chest CT (if screening visit chest X-ray demonstrated metastatic chest disease) and bone scan will be repeated at day 85/week 13 visit and every 12 weeks thereafter. Imaging may be performed at any time to confirm suspected disease progression. Assessment will include tumor measurements for target lesions and nontarget lesions and assessment for any new lesions. An overall assessment will be documented for each time point evaluation. At the end of the study for each subject, an overall best response will be documented.

Study films should be read on site and also submitted in digital format to the sponsor designated facility in case independent central review is required after the end of study. The initial imaging/scanning technique should be applied for the duration of the study for the subject and assessed by the same site designated reader, whenever possible.

Radiographic disease progression is defined as progressive disease by RECIST version 1.1 for soft tissue disease or by appearance of 2 or more new lesions on bone scan. The documentation and confirmation required for the determination of radiographic progression is listed in [Table 2].

Table 2 Protocol-specified Documentation for Radiographic Evidence of Disease Progression

Date Progression Detected (Visit)†	Criteria for Progression	Criteria for Confirmation of Progression (Requirement and Timing)	Criteria for Documentation of Disease Progression on Confirmatory Scan
Week 13	Bone lesions: ≥ 2 new lesions compared to **baseline** bone scan	Timing: ≥ 6 weeks after progression identified or at week 25 visit	≥ 2 new bone lesions on bone scan compared to week 13 scan (≥ 4 new lesions compared to **baseline** bone scan)
	Soft tissue lesions: progressive disease on CT or MRI by RECIST v1.1	No confirmatory scan required for soft tissue disease progression	Not applicable
Week 25 or Later	Bone lesions: ≥ 2 new lesions on bone scan compared to best response on treatment	No confirmatory scan required	Not applicable
	Soft tissue lesions: progressive disease on CT or MRI by RECIST v1.1	No confirmatory scan required for soft tissue disease progression	Not applicable

CT: computed tomography; MRI: magnetic resonance imaging; RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1

† Progression detected by bone scan at an unscheduled visit prior to week 25 will require the same criteria for documentation of disease progression as week 13 with a confirmatory scan at least 6 weeks later or at the next scheduled scan.

Study drug treatment should be continued as long as the subject is tolerating the study drug and continues ADT until radiographic disease progression is documented as outlined in [Table 2] or the initiation of new antineoplastic therapy for treatment of prostate cancer. It is recommended that subjects remain on study treatment until radiographic disease progression is confirmed. Subjects who discontinue study treatment without confirmed radiographic progression will continue to be scanned every 12 weeks until radiographic progression is confirmed by investigator assessment or the required number of PSA progression events for the final analysis is reached.

5.3.1.3 Subject Reported Outcomes

Subject reported outcomes will be collected according to the schedule of assessments during onsite visits [Table 1].

BPI-SF

The BPI-SF pain questionnaire is a validated instrument that is a subject self-rating scale assessing level of pain, effect of the pain on activities of daily living and analgesic use. The BPI used in this study is the short form and contains 9 questions. The BPI uses simple numeric rating scales from 0 to 10.

QLQ-PR25

The QLQ-PR25 is a 25-item module designed to assess QoL in prostate cancer subjects. The extent of occurrence of 25 defined symptoms related to bowel, bladder and hormones as well as interest in and occurrence of sexual activity are rated by selecting 1 of 4 categories ranging from not at all to very much.

EQ-5D-5L

The EQ-5D-5L is a QoL instrument for self-reported assessment of 5 domains of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each domain is rated by selecting 1 of 5 standardized categorizations ranging from no problem to extreme problem. The final question is a visual analogue scale to rank health status from best health imaginable to worst health imaginable.

FACT-P

The FACT-P questionnaire is a multi-dimensional, self-reported QoL instrument specifically designed for use with prostate cancer subjects. It consists of 27 core items that assess subject function in 4 domains: physical, social/family, emotional, and functional wellbeing, which is further supplemented by 12 site-specific items to assess for prostate-related symptoms. Each item is rated on a 0 to 4 Likert-type scale.

5.4 Safety Assessment

5.4.1 Vital Signs

Routine vital signs, including blood pressure, pulse and temperature will be assessed at the screening visit, at every clinic visit while on study drug and at the safety follow-up visit.

5.4.2 Laboratory Assessments

Routine laboratory samples for hematology, chemistry and PSA will be collected at the screening visit, at every clinic visit while on study drug and at the safety follow-up visit. Testosterone will be collected at week 13 and every subsequent 12 weeks while on study drug. Other laboratory assessments will be collected according to the schedule of assessments [Table 1]. PSA will be analyzed at sponsor designated central laboratory, other tests will be analyzed by each site itself. Analytes included are identified in [Table 3].

Table 3 Laboratory Assessments

Hematology	Biochemistry	Other
Red blood cell count White blood cell count White blood cell differential Hemoglobin Hematocrit Platelet count	Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Blood urea nitrogen Blood urea Calcium Creatinine Glucose Phosphorus Potassium Sodium Total bilirubin Total protein	Testosterone PSA

Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator/subinvestigator who is a qualified physician. Since a local or other clinical laboratory was used for hematology, biochemistry, testosterone and the urgent management of an AE, the reference ranges of the laboratory were provided to the sponsor or delegated CRO.

5.4.3 Physical Examination

Complete physical examination will be performed at the screening visit to assess weight, height, general appearance, skin, eyes, ears, nose, throat, neck, cardiovascular, respiratory, gastrointestinal, musculoskeletal, neurologic status, mental status, lymphatic and genitourinary systems.

A brief physical examination with weight will be performed at day 1, all subsequent clinic visits while on study drug and at the safety follow-up visit. New or worsening clinically significant findings on physical examination will be recorded as AEs if they meet the criteria in [Section 5.5.1 Definition of Adverse Events].

5.4.4 Electrocardiogram

Standard 12-lead ECGs will be performed at the local institution and interpreted by the local institution's medically trained staff. ECGs will be performed at screening, day 1 and the safety follow-up visit. Parameters that include heart rate, PR interval, RR interval, QRS interval, QT interval, and interpretation and clinical significance as judged by the investigator will be collected.

ECGs should be obtained after the subject has rested quietly and is awake in a fully supine position (or semirecumbent if supine is not tolerated) for 10 minutes. It is recommended that ECG reports are printed in duplicate and photocopied to prevent fading.

5.4.5 Imaging

See [Section 5.3.1.2 CT/MRI and bone scan] for detailed information regarding imaging.

5.4.6 Order of Assessments

Not applicable.

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events

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

In order to identify any events that may be associated with study procedures and could lead to a change in the conduct of the study, Astellas collects AEs even if the subject has not received study drug treatment. AE collection begins after the signing of the informed consent for the double-blind period and will be collected until 30 days after the last dose of study drug (including the double-blind period and open-label phase if applicable), or initiation of a new therapy for prostate cancer, or the subject is determined to be a screen failure, whichever occurs first. During the post treatment follow-up period, only symptomatic skeletal events need to be reported.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

Some sites may have additional local requirements for events that are required to be reported as AEs or in an expedited manner similar to a SAE. In these cases, it is the investigator's responsibility to ensure these AEs or other reporting requirements are followed and the information is appropriately recorded in the electronic case report form (eCRF) accordingly.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical examination) 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.

5.5.1.1 Abnormal Laboratory Findings

Any abnormal laboratory test result (e.g. hematology, clinical chemistry, or urinalysis) or other safety assessment (e.g., ECGs, radiographic scans, vital signs measurements, physical examination), including those that worsen from baseline, that is considered to be clinically significant in the medical and scientific judgment of the investigator and not related to underlying disease, is to be reported as an (S)AE.

Any clinically significant abnormal laboratory finding or other abnormal safety assessment which is associated with the underlying disease does not require reporting as an (S)AE, unless judged by the investigator to be more severe than expected for the subject's condition.

Repeating an abnormal laboratory test or other safety assessment, in the absence of any of the above criteria, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

5.5.1.2 Potential Cases of Drug-Induced Liver Injury

Refer to [Appendix 12.5 Liver Safety Monitoring and Assessment] for detailed instructions on Drug Induced Liver Injury (DILI). Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent or with abnormal elevations in total bilirubin that meet the criteria outlined in [Appendix 12.5 Liver Safety Monitoring and Assessment], in the absence of other causes of liver injury, are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and are always to be considered important medical events and reported per [Section 5.5.5 Reporting of Serious Adverse Events].

5.5.1.3 Disease Progression and Study Endpoints

Under this protocol, the following event(s) will not be considered as an(S)AE:

- Disease Progression: events including defined study endpoints that are clearly consistent with the expected pattern of progression of the underlying disease are not to be recorded as AEs. These data will be captured as efficacy assessment data as outlined in Section 5.3. If there is any uncertainty as to whether an event is due to anticipated disease progression and/or if there is evidence suggesting a causal relationship between the study drug and the event, it should be reported as an (S)AE. All deaths up to 30 days after the last dose of study drug must be reported as an SAE, even if attributed to disease progression. And this event is recorded as an SAE with 'disease progression' as the reported term.
- Pre-planned and elective hospitalizations or procedures for diagnostic, therapeutic, or surgical procedures for a pre-existing condition that did not worsen during the course of the clinical trial. These procedures are collected per the eCRFs Completion Guidelines.

5.5.2 Definition of Serious Adverse Events (SAEs)

An AE is considered "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 subject 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 in-subject hospitalization (except for planned procedures as allowed per study) or leads to prolongation of hospitalization (except if prolongation of planned hospitalization is not caused by an AE). Hospitalization for treatment/observation/examination caused by AE is to be considered as serious;
- Other medically important events. (defined in paragraph below)

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 subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, usually are 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.

5.5.3 Criteria for Causal Relationship to the Study Drug

A medically qualified investigator is obligated to assess the relationship between the study drug and each occurrence of each (S)AE. This medically qualified investigator will use medical judgment as well as the Reference Safety Information (RSI) (refer to Section 1.3) to determine the relationship. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The medically qualified investigator is requested to provide an explanation for the causality assessment for each (S)AE and must document in the medical notes that he/she has reviewed the (S)AE and has provided an assessment of causality.

Following a review of the relevant data, the causal relationship between the study drug and each (S)AE will be assessed by answering '**yes**' or '**no**' to the question "**Do you consider that there is a reasonable possibility that the event may have been caused by the study drug**".

When making an assessment of causality, the following factors are to be considered when deciding if there is evidence and/or arguments to suggest there is a 'reasonable possibility' that an (S)AE may have been caused by the study drug (rather than a relationship cannot be ruled out) or if there is evidence to reasonably deny a causal relationship:

- Plausible temporal relationship between exposure to the study drug and (S)AE onset and/or resolution. Has the subject actually received the study drug? Did the (S)AE occur in a reasonable temporal relationship to the administration of the study drug?
- Plausibility; i.e., could the event be caused by the study drug? Consider biologic and/or pharmacologic mechanism, half-life, literature evidence, drug class, preclinical and clinical study data, etc.
- Dechallenge/Dose reduction/Rechallenge:
    - Did the (S)AE resolve or improve after stopping or reducing the dose of the suspect drug? Also consider the impact of treatment for the event when evaluating a dechallenge experience.
    - Did the (S)AE reoccur if the suspected drug was reintroduced after having been stopped?
- Laboratory or other test results; a specific lab investigation supports the assessment of the relationship between the (S)AE and the study drug (e.g., based on values pre-, during and post-treatment)
- Available alternative explanations independent of study drug exposure; such as other concomitant drugs, past medical history, concurrent or underlying disease, risk factors including medical and family history, season, location, etc. and strength of the alternative explanation

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the medically qualified investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor. With limited or insufficient information about the event to make an informed medical judgment and in absence of any indication or evidence to establish a causal relationship, a causality assessment of 'no' is to be considered. In such instance, the investigator is expected to obtain additional information regarding the event as soon as possible and to re-evaluate the causality upon receipt of additional information. The medically qualified investigator may revise his/her assessment of causality in light of new information regarding the SAE and shall send an SAE follow-up report and update the eCRF with the new information and updated causality assessment.

5.5.4 Criteria for Defining the Severity of an Adverse Event

AEs, including abnormal clinical laboratory values, will be graded using the NCI-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

5.5.5 Reporting of Serious Adverse Events

The collection of AEs and the expedited reporting of SAEs will start following the signing of the informed consent for the double-blind period and will be collected until 30 days after the last dose of study drug (including the double-blind period and open-label phase if applicable), or initiation of a new therapy for prostate cancer, or the subject is determined to be a screen failure, whichever occurs first. During the post treatment follow-up period, only symptomatic skeletal events need to be reported.

In the case of a SAE, the investigator must contact the sponsor by fax or email immediately (within 24 hours of awareness). The investigator must complete and submit an SAE Worksheet containing all information that is required by local and /or regional regulations to the sponsor by email or fax immediately (within 24 hours of awareness).

The SAE worksheet must be signed by a medically qualified investigator (as identified on Delegation of Authority Log). Signature confirms accuracy and completeness of the SAE data as well as the investigator causality assessment including the explanation for the causality assessment.

If the SAE is associated with emergency unblinding as outlined in [Section 4.4.4 Breaking the treatment code for Emergency] this is to be recorded on the SAE worksheet. Within the SAE worksheet, the investigator is to include when unblinding took place in association with the SAE.

For contact details, see [Section II Contact Details of Key Sponsor's Personnel]. Fax or email the SAE/Special Situations Worksheet to:

Astellas Pharma Global Development Inc.

Pharmacovigilance

North America fax number: 1-888-396-3750

North America alternate fax number: 1-847-317-1241

International fax number: +44 800-471-5263

Email: safety-us@astellas.com

Copy: acn_pv@astellas.com

If there are any questions, or if clarification is needed regarding the SAE, 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, SAE/Special Situation Worksheet and on the eCRF.

The following minimum information is required:

- International study number (ISN)/Study number
- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug (including reason), and
- The drug or blinded regimen provided (if any)

The sponsor or sponsor's designee will medically evaluate the SAE and determine if the report meets the requirements for expedited reporting based on seriousness, causality, and expectedness of the events (e.g. Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting) according to current local/regional regulatory requirements in participating countries. The sponsor or sponsor's designee will submit expedited safety reports (e.g., IND Safety Reports, SUSAR, CIOMS-I) to Competent Authorities (CA) and concerned Ethics Committee (cEC) per current local regulations, and will inform the investigators of such regulatory reports as required. Investigators must submit safety reports as required by their Institutional Review Board (IRB)/local Independent Ethics Committee (IEC) within timelines set by regional regulations (cFDA) where required. Documentation of the submission to and receipt by the IRB/local IEC of expedited safety reports should be retained by the site.

The sponsor will notify all investigators responsible for ongoing clinical studies with the study drug of all SUSARs which may require submission per local requirements to the IRB/local IEC. The investigators should provide written documentation of IRB/local IEC notification for each report to the sponsor.

The investigator may contact the sponsor's Medical Monitor/Study Physician for any other problem related to the safety, welfare or rights of the subject.

5.5.6 Follow-up of Adverse Events

All AEs occurring during or after the subject 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 by the investigator.

If after the protocol defined AE collection period [see Section 5.5.1 Definition of Adverse Event], an AE progresses to a SAE, or the investigator learns of any (S)AE including death, where he/she considers there is reasonable possibility it is related to the study drug treatment or study participation, the investigator must promptly notify the sponsor.

5.5.7 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 12.6 Common Serious Adverse Events] for reference. The list does NOT change the investigator's 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 note that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common SAEs" as specified in [Appendix 12.6 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 5.5.5 Reporting of Serious Adverse Events].

5.5.8 Special Situations

Certain Special Situations observed in association with the study drug(s), such as incorrect administration (e.g., wrong dose of study drug, comparator, or background therapy) are collected in the eCRF, as Protocol Deviation per [Section 8.3 Major Protocol Deviations] or may require special reporting, as described below. These Special Situations are not considered AEs, but do require to be communicated to Astellas as per the timelines defined below.

If a Special Situation is associated with, or results in, an AE, the AE is to be assessed separately from the Special Situation and captured as an AE in the eCRF. If the AE meets the definition of a SAE, the SAE is to be reported as described in [Section 5.5.5 Reporting of Serious Adverse Events] and the details of the associated Special Situation are to be included in the clinical description on the SAE worksheet.

The Special Situations are:

- Pregnancy
- Medication Error, Overdose and "Off label use"
- Misuse/abuse
- Occupational exposure

- Suspected Drug-Drug interaction

5.5.8.1 Pregnancy

If a female partner of a male subject becomes pregnant during the study dosing period or within 90 days from the discontinuation of dosing, the investigator should report the information to the sponsor as if it is an SAE. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information.

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 is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination.

5.5.8.2 Medication Error, Overdose and "Off-Label Use"

If a Medication Error, Overdose or "Off label Use" (i.e., use outside of what is stated in the protocol) is suspected, refer to [Section 8.3 Major Protocol Deviations]. Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in [Section 5.5.5 Reporting of Serious Adverse Events] together with the details of the medication error, overdose and/or "Off-Label Use".

An overdose is defined as any dose greater than the protocol specified dose of enzalutamide 160 mg once daily. In the event of an enzalutamide overdose, the study drug should be stopped and subject should receive supportive care and monitoring. The Medical Monitor should be contacted.

Neither the effects of overdose of enzalutamide or an antidote to overdose are known. Subjects may be at increased risk of seizures following an overdose of enzalutamide.

5.5.8.3 Misuse/Abuse

If misuse or abuse of the study drug(s) is suspected, the investigator must forward the Special Situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in [Section 5.5.5 Reporting of Serious Adverse Events] together with details of the misuse or abuse of the study drug(s).

5.5.8.4 Occupational Exposure

If occupational exposure (e.g. inadvertent exposure to the study drug(s) of site staff whilst preparing it for administration to the patient) to the study drug(s) occurs, the investigator must forward the Special Situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs occurring to the individual associated with or resulting from the Special Situation are to be reported on the Special Situations worksheet.

5.5.8.5 Suspected Drug-Drug Interaction

If a suspected drug-drug interaction associated with the study drug(s) is suspected, the investigator must forward the Special Situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in [Section 5.5.5 Reporting of Serious Adverse Events] together with details of the suspected drug-drug interaction.

5.5.9 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.

The investigator will also inform the subjects, who will be required to sign an updated informed consent form in order to continue in the clinical study.

5.5.10 Urgent Safety Measures

An Urgent Safety Measure (USM) is an intervention, which is not defined by the protocol and can be put in place with immediate effect without needing to gain prior approval by the sponsor, relevant Competent Authorities, IRB/IEC, where applicable, in order to protect study participants from any immediate hazard to their health and/or safety. Either the investigator or the sponsor can initiate an USM. The cause of an USM can be safety, product or procedure related.

5.5.11 Reporting Urgent Safety Measures

In the event of a potential USM, the investigator must contact the Astellas Study Physician (within 24 hrs of awareness). Full details of the potential USM are to be recorded in the subject's medical records. The sponsor may request additional information related to the event to support their evaluation.

If the event is confirmed to be an USM the sponsor will take appropriate action to ensure the safety and welfare of the patients. These actions may include but are not limited to a change in study procedures or study treatment, halting further enrollment in the trial, or stopping the study in its entirety. The sponsor or sponsor's designee will notify CA and cEC within the timelines required per current local regulations, and will inform the investigators as required. When required, investigators must notify their IRB/IEC within timelines set by regional regulations.

5.6 Test Drug Concentration

Not applicable.

5.7 Other Measurements, Assessments or Methods

Not applicable.

5.8 Total Amount of Blood

The total amount of blood to be drawn for a subject will vary depending on the course of their disease and their duration on study treatment. At any time during the study, if laboratory values are determined to be abnormal, additional blood samples may be required for monitoring subject safety. The maximum amount of blood estimated to be collected over the protocol outlined visits from screening visit through day 85/week 13 visit is approximately 100 mL. Approximately 10 mL will be drawn at each subsequent study visit while on study drug.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s) From Study Treatment

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

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

If a subject is discontinued from the study with an ongoing AE or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until the condition stabilizes or no longer is clinically significant.

Subject will be discontinued from the study drug treatment if any of the following occur:

- Any AE that is intolerable to the subject which cannot be ameliorated by the use of adequate medical intervention and/or dose reduction or that in the opinion of the investigator would lead to undue risk to the subject if dosing is continued.
- Subject who experiences a seizure or any condition that significantly predisposes the subject to seizure such as brain metastasis or clinically evident stroke.
- Subject who experiences a confirmed event of PRES by brain imaging, preferably by MRI.

- Subject initiates an investigational agent or new therapy for prostate cancer.
- Subject who has evidence of radiological disease progression as confirmed and in the judgment of the investigator is no longer deriving clinical benefit.
- Subject has discontinued ADT (LHRH agonist/antagonist) and has a testosterone value in the noncastrate range (> 50 ng/dL).
- Dose interruptions >14 consecutive days. Dose interruptions for subjects who are deriving clinical benefit from treatment may be extended beyond 14 days after sponsor's approval. Dose interruptions of study drug ≤ 14 days consecutive are permitted at any point during treatment.
- Subject who is, in the opinion of the investigator or the Medical Monitor, noncompliant with the protocol requirements.
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Subject withdraws consent for the study.

Subject will be discontinued from the study follow-up (Safety or Long-term Follow-up) if any of the following occur:

- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Subject withdraws consent for further follow-up.
- Death.
- Study termination by the sponsor.

6.1.1 Lost to Follow Up

Every reasonable effort is to be made to contact any subject lost to follow up during the course of the study to complete study related assessments, record outstanding data, and retrieve study drug (via telephone, letter, email, etc.) at a minimum frequency of once weekly for at least 3 weeks.

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor.

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

A statistical analysis plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures to be produced. The SAP will be finalized before the database lock at the latest. Any changes from the analyses planned in SAP will be justified in the clinical study report.

Prior to database lock, a Final Review of Data and Tables, Listings and Figures Meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database lock.

In general, all data will be summarized with descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints.

7.1 Sample Size

As originally planned, approximately 180 Chinese subjects will be randomized in the study. (120 subjects in enzalutamide + ADT arm and 60 subjects in placebo + ADT arm).

The final analysis of TTPP will be conducted with a planned 75 PSA progression events based on the following considerations:

- A target HR is 0.5. The expected median TTPP for the ADT arm is 9 months as measured from the date of randomization. A target HR of 0.5 corresponds to approximately 100% increase in median TTPP for the enzalutamide plus ADT arm relative to the placebo plus ADT arm (approximately 18 versus 9 months, with 10% dropout rate).
- The planned 75 PSA progression events provides approximately 80% power to detect a target HR of 0.5 based on a 2-sided log-rank test and overall significance level of 0.05. PSA progression is defined as a ≥ 25% increase and an absolute increase of ≥ 2 µg/L (2 ng/mL) above the nadir (i.e., lowest PSA value observed post baseline or at baseline), which is confirmed by a second consecutive value at least 3 weeks later. (Prostate Cancer Clinical Trials Working Group 3 criteria) (tested by central laboratory)
- There will be 1 interim analysis at 80% of the total planned events (about 60 PSA progression events), providing 61% power to demonstrate superiority at a 2-sided alpha of 0.0244.

7.2 Analysis Sets

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

7.2.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population is defined as all subjects who were randomized in this

study. The ITT population will be analyzed by treatment arm as randomized (i.e., treatment arm based on randomization assignment). The ITT population will be used to conduct efficacy analyses. For the ORR, only subjects with measurable disease at baseline will be included in the analysis.

7.2.2 Safety Population

The safety population is defined as all randomized subjects who received at least 1 dose of study drug. The safety population will be analyzed by treatment arm as treated (i.e., based on the treatment the subject actually received rather than the treatment to which the subject was randomized). The safety population will be used to conduct safety analyses.

7.3 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized by treatment group for the ITT population. Descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum for continuous endpoints, and frequency and percentage for categorical endpoints.

7.4 Analysis of Efficacy

7.4.1 Analysis of Primary Endpoint

7.4.1.1 Primary analysis

Time to PSA progression (TTPP) is defined as a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir (i.e., lowest PSA value observed postbaseline or at baseline), which is confirmed by a second consecutive value at least 3 weeks later.

The effect of enzalutamide plus ADT compared to ADT will be tested using a stratified logrank test. The benefit of enzalutamide plus ADT compared to ADT will be summarized by a single HR with its 95% CI based on the Cox regression model. Kaplan-Meier curves will be used to estimate the distribution of the duration of time to PSA progression. Median duration of time to PSA progression will be estimated using the corresponding 50% percentile of the Kaplan-Meier estimates. A 2-sided 95% CI will be provided for these estimates.

There are 2 planned analyses, one final analysis at the total planned 75 PSA progression events and one interim analysis at 80% of the total planned events (about 60 PSA progression events). TTPP will be formally tested at both interim analysis and final analysis at 2-sided 0.0244 and 0.0429 significance level, respectively, for efficacy according to the O'Brien-Fleming boundary as implemented by Lan-DeMets alpha spending function [Lan-DeMets, 1983]. Data cut-off dates will be set when the planned number of events is reached for the interim and final analyses. If the exact number of events at interim and final analyses are different than planned, the significance level will be adjusted accordingly, based on the O'Brien-Fleming method with a Lan-DeMets alpha spending function. The family-wise type I error rate for this study is strongly controlled at 5% (2-sided) that allows the study to declare positive on primary endpoint TTPP on the ITT population.

7.4.1.2 Sensitivity Analysis

Sensitivity will be conducted to the primary endpoint, the detailed information will be described in the SAP.

7.4.1.3 Subgroup Analysis

Subgroup analyses of TTPP will be conducted to assess the consistency of the treatment effect across the subgroups.

7.4.2 Analysis of Secondary Endpoints

rPFS:

rPFS is defined as the time from randomization to the first objective evidence of radiographic disease progression as assessed or death (defined as death from any cause within 24 weeks from study drug discontinuation), whichever occurs first.

Radiographic disease progression is defined as progressive disease by RECIST version 1.1 for soft tissue disease or by appearance of 2 or more new lesions on bone scan. The analysis method will be the same as TTPP.

Time to first SSE:

Time to first SSE is defined as the time from randomization to the occurrence of the first SSE. SSE is defined as radiation or surgery to bone, clinically apparent pathological bone fracture or spinal cord compression. The analysis method will be the same as for time to PSA progression.

Time to castration resistance:

Castration resistance is defined as occurrence of radiographic disease progression, PSA progression or SSE with castrate levels of testosterone (< 50 ng/dL). Time to castration resistance is defined as the time from randomization to the first castration-resistant event (radiographic disease progression, PSA progression or SSE), whichever occurs first. The analysis method will be the same as for time to PSA progression.

PSA Response ≥ 50%, PSA Response ≥ 90%:

PSA response ≥ 50% is defined as ≥ 50% reductions in PSA level from baseline to the lowest post-baseline PSA result as determined by the central laboratory, with a consecutive assessment conducted at least 3 weeks later to confirm the PSA response. The same logic for PSA response ≥90%. The serum PSA response rate will be summarized at each time point. Waterfall plots of the rate of change from baseline will be constructed. PSA response ≥ 50% and ≥ 90% will be calculated by treatment group for subjects with PSA values at the baseline assessment and at least 1 post-baseline assessment.

Time to initiation of a new antineoplastic therapy:

All antineoplastic therapies, including cytotoxic and hormone therapies, will be considered for this endpoint. Time to initiation of a new antineoplastic therapy is defined as the time from

randomization to the initiation of antineoplastic subsequent to the study treatments. The analysis method will be the same as for time to PSA progression.

PSA undetectable rate:

The undetectable level of PSA is defined as < 0.2 ng/mL. The PSA undetectable rate is defined as the percentage of subjects with detectable (≥ 0.2 ng/mL) PSA at baseline, which becomes undetectable (< 0.2 ng/mL) during study treatment and will be summarized at each time point. Only subjects with detectable PSA at baseline will be included in this analysis.

ORR:

The ORR is defined as the percentage of subjects with measurable disease at baseline who achieved a complete or partial response in their soft tissue disease using the RECIST version 1.1 criteria on CT/MRI, and for bone lesions on bone scans. Only subjects with detectable lesions will be included in this analysis.

7.4.3 Analysis of Exploratory Endpoints

Time to deterioration of QoL:

A deterioration of QoL is defined as a 10-point decrease in the total FACT-P score from baseline. Time to deterioration of QoL is defined as time from randomization to a 10-point reduction of the FACT-P total score. The analysis method will be the same as for time to PSA progression.

Time to pain progression:

Pain progression is defined an increase of ≥ 30% from baseline in the average BPI-SF item scores. Time to pain progression is defined as time from randomization to an increase of 30% in pain severity score from baseline using the BPI-SF. The analysis method will be the same as for time to PSA progression.

Time to event endpoints such as time to PSA progression, rPFS, time to first SSE, time to castration resistance, time to deterioration of QoL, time to pain progression and time to initiation of new antineoplastic therapy will be analyzed using the stratified log-rank test. The stratified Cox Regression analysis, with just treatment effect as a factor in the model, will be used to estimate the HR and the associated 95% CI. The median will be estimated using the Kaplan-Meier method.

The proportion endpoints such as PSA Response ≥ 50%, PSA Response ≥ 90%, PSA undetectable rate and ORR will be analyzed using the stratified Cochran-Mantel-Haenszel score test.

7.5 Analysis of Safety

Safety analyses will be conducted using the safety population and summarized by treatment arms as treated.

Baseline laboratory results will be summarized using descriptive statistics by treatment arms. Worst toxicity grades per subject will be tabulated for selected AEs and laboratory analytes.

Clinical safety data (including AEs, grade 3 and 4 hematologic and nonhematologic events, clinical laboratory evaluations, vital signs, ECGs and physical examinations) will be summarized by treatment groups using descriptive statistics or frequency distribution as appropriate.

Treatment-emergent period is defined as the duration of the study treatment plus 30 days. AEs occurring in this period are termed treatment-emergent AEs.

Duration of treatment and total dose administered will be summarized by treatment groups. In addition, the number and percentage of subjects with dose reduction will be tabulated.

7.5.1 Adverse Events

Treatment-emergent AEs will be coded to system organ class and preferred terms using MedDRA and graded using NCI-CTCAE (version 4.03).

Treatment-emergent AEs will be tabulated alphabetically by system organ class and by preferred terms within system organ class.

Treatment-emergent AEs will be presented within each system organ class by preferred term, by relationship to study drug and by severity (NCI-CTCAE grade). Treatment-emergent AEs leading to permanent discontinuation of study drug, SAEs and SAEs by NCI-CTCAE grade will be summarized.

7.5.2 Laboratory Assessments

Clinical laboratory evaluations (including hematology and serum chemistry) will be presented for each visit using descriptive statistics (n, mean, SD, median, minimum and maximum values). Change from baseline will also be presented. Shift analysis tables will present the shift from baseline for using NCI-CTCAE grade and lab reference range indicator. All clinically significant abnormal laboratory values will be recorded as AEs and graded using NCI-CTCAE guidelines. A listing of subject laboratory values will be provided.

7.5.3 Vital Signs

Descriptive statistics (n, mean, SD, median, minimum and maximum) will be presented for each vital sign at each time point and the change from baseline.

7.5.4 Physical Examination

All clinically significant abnormal findings will be recorded as medical history or AEs. AEs will be graded using NCI-CTCAE guidelines.

7.5.5 Routine 12-lead Electrocardiograms

Overall ECG interpretation will be summarized for each time point. A shift analysis table showing change from baseline in overall ECG (normal, abnormal not clinically significant, and abnormal clinically significant) will be provided.

7.5.6 Continuous 12-Lead Electrocardiogram

Not applicable.

7.5.7 Imaging

rPFS data collected based on CT/MRI and bone scan images will be summarized by treatment group and time point.

7.5.8 Concentration-Response Relationship Analysis

Not applicable.

7.6 Analysis of Pharmacokinetics

Not applicable.

7.7 Major Protocol Deviations and Other Analyses

Major protocol deviations as defined in [Section 8.3 Major Protocol Deviations] will be summarized for all randomized subjects by treatment group and total as well as by site. A data listing will be provided by site and subject.

The major 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 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment,

7.8 Interim Analysis

An interim analysis is planned to occur after approximately 60 PSA progression events (about 80% of the total planned events) are observed. TTPP will be tested for efficacy according to the O'Brien-Fleming boundary as implemented by Lan-DeMets alpha spending function [Lan-DeMets, 1983]. The IDMC may recommend terminating the trial at the interim analysis based on statistically significant TTPP results favoring enzalutamide. In case IDMC recommend continuing the trial after the interim analysis, the final TTPP analysis will be conducted when total PSA progression events reach 75. Data cut-off dates will be set when the planned number of events is reached for the interim and final analyses. If the exact number of events at interim and final analyses are different than planned, the significance level will be adjusted accordingly, based on the O'Brien-Fleming method with a Lan-DeMets alpha spending function.

The interim analysis will be conducted by independent data analysis group (DAC) with randomized treatment assignments and reviewed by the IDMC. The full procedures for IDMC and interim analysis will be described in a separate IDMC charter and Interim Analysis Plan.

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

Imputation for missing data, if applicable, will be addressed in the SAP.

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 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 within 5 days after the subject visit.

The investigator or site designee is responsible to ensure 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.

Subject reported outcomes questionnaires will be completed by the subject on an electronic device during onsite visits. Information completed by the subject on the electronic device will be automatically uploaded to a central website. The investigator or site designee should review the data status for completion while the subject is at the site. The questionnaire data will be transferred electronically to the sponsor or designee at predefined intervals during the study. The vendor will provide the sponsor or designee with a complete and clean copy of the data. If a subject cannot visit site to perform study procedure, subject does not need to use the paper questionnaire to collect “Patient Reported Outcome”.

PSA tests are performed at the sponsor designated central laboratory. The 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. The other blood tests are performed independently by each site and will be entered into eCRF by each site and its delegate study person at predefined intervals during this study.

Study films (computed tomography [CT]/magnetic resonance imaging [MRI] and bone scan) should be read on site and also be submitted in digital format to the Sponsor-designated facility and enter into eCRF in case independent central review is required after the end of study.

8.2 Screen failures

For screen failures, the minimum demographic data (gender, birth date or age, race and informed consent date) and reason for screen failure will be collected in the eCRF and the screen failure log, if applicable. This information will be entered into the study database.

8.2.1 Re-Screening

Subjects who have failed screening are allowed to be re-screened once after consultation with the medical monitor. A new subject number will be assigned. Subjects have to re-consent to the study and all screening procedures must be repeated, with the exception of the radiologic imaging procedure to confirm eligibility if the scan is within 6 weeks prior to the first dose of study treatment (Day 1).

Laboratory values re-tested within the original 28-day screening period are not considered re-screening and no new subject number will be assigned.

8.3 Major Protocol Deviations

A major 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 subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to trial subjects.

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

The major protocol deviation criteria are 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 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

When a major deviation from the protocol is identified for an individual subject, 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 subject to determine subject continuation in the study.

If a major deviation impacts the safety of a subject, 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.

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.

9 END OF TRIAL

The end of trial in all participating sites is defined as the last subject's last visit or last subject's last contact, whichever is longer.

10 STUDY ORGANIZATION

10.1 IDMC

The IDMC primary responsibilities will be assessing the efficacy of the study treatment(s), and safety data will also be considered at the same time when IDMC makes recommendations

based on the efficacy data from the benefit-risk perspective. Members of the IDMC will be independent from the Sponsor and also will not participate as investigators in the trial. An IDMC consisting of experts in prostate cancer, and statistics will mainly evaluate the efficacy of the trial at the planned interim analysis which will occur after at least 60 events (about 80% of the total planned events). The IDMC may recommend to the sponsor whether the trial should be terminated or continue unchanged based on interim analysis.

Further details on the composition and responsibility of the IDMC will be outlined in a separate charter.

10.2 Other study Organization

Not applicable.

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12 APPENDICES

12.1 Ethical, Regulatory, and Study Oversight Considerations

12.1.1 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.

12.1.2 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 ICF and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) 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 subject 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 IRB/IEC approval before implementation, except for changes necessary to eliminate an immediate hazard to subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, and local regulations.

12.1.3 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 nonsubstantial 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 subject 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 informed consent, 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.

12.1.4 Informed Consent of Subjects

12.1.4.1 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject 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 subject, the informed consent statement will be reviewed and signed and dated by the subject 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 subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The signed consent forms 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.

12.1.4.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

1. The investigator or his/her representative will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue to participate in the study (e.g., report of serious drug adverse drug reaction). The communication must be documented in the subject's medical records and must document whether the subject is willing to remain in the study or not.
2. 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 subject on all updated ICFs throughout their participation in the study. The investigator or his/her designee must reconsent subjects 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 subject should sign and date the ICF. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must be made in the subject's records documenting the reconsent process.

12.1.5 Source Documents

Source data must be available at the site to document the existence of the study subjects 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 subject.

The investigator is responsible for ensuring the source data are attributable, legible, contemporaneous, original, accurate and complete whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, achieved, retrieved or transmitted electronically via computerized systems (and/or other kind of electric devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records, protocol related assessments, adverse event tracking, and/or drug accountability.

Paper records from electronic systems used in place of electronic format must be certified copies. A certified copy must be an exact copy and must have all the same attributes and information as the original. Certified copies must include signature and date of the individual completing the certification. Certified copies must be a complete and chronological set of study records (including notes, attachments, and audit trail information (if applicable). All printed records must be kept in the subject file and available for archive.

12.1.6 Record Retention

The investigator will archive all study data (e.g., subject identification code list, source data, eCRFs and investigator's file and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (Five years after NDA approval). The sponsor will notify the site/investigator if the NDA is approved or if the IND is discontinued. 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 subjects' medical records and/or study progress notes. All data will be entered into the eCRFs.

12.1.7 Subject Confidentiality and Privacy

Individual subject 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 subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

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

All individuals and organizations involved in the study must pay very careful attention to protect subjects’ privacy with appropriate measures, for example, by prohibiting the use of any private information that may identify a subject (e.g., name or address). These details shall be processed in accordance with the applicable local and regional laws.

Even though any individuals involved in the study, including the study monitors and auditors, may get to know matters related to subject's privacy due to direct access to source documents, or from other sources, they may not leak the content to third parties.

The sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials will identify subject 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 agrees to comply and process personal data in accordance with all applicable privacy laws and regulations, including, without limitation, the Personal Information Protection Law in Japan and Privacy laws in the US.

12.1.8 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.

12.1.9 Signatory Investigator for Clinical Study Report

ICH E3 guidelines 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.

12.2 Procedure for Clinical Study Quality Control

12.2.1 Clinical Study Monitoring

The sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and 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.

12.2.2 Direct Access to Source Data/Documents

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

12.2.3 Data Management

Data Management will be coordinated by the Data Management Team of the sponsor in accordance with the SOPs for data management. All study-specific processes and definitions will be documented by Data Management. eCRF completion will be described in the eCRF instructions. Coding of medical terms and medications will be performed using MedDRA and World Health Organization (WHO) Drug Dictionary, respectively.

12.2.4 Quality Assurance

The sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented, recorded and reported in compliance with the protocol, GCP and applicable regulatory requirement(s).

The sponsor or sponsor's designee may arrange to audit the clinical study at any or all investigational sites and facilities. The audit may include on-site review of regulatory documents, CRFs, and source documents. Direct access to these documents will be required by the auditors.

12.3 Contraception Requirements

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

A sexually active male subject with female partner(s) who is of childbearing potential is eligible if:

- Agrees to use a male condom starting at screening and continue throughout the study treatment and for at least 3 months after the last dose of study drug. If the male subject has not had a vasectomy or is not sterile at least 6 months prior to screening as defined below his female partner(s) is utilizing 1 form of highly effective birth control* per locally accepted standards starting at screening and continue throughout study treatment and for at least 3 months after the male subject receives his last dose of study drug. [a]

*Highly effective forms of birth control include:

- Consistent and correct usage of established hormonal contraceptives that inhibit ovulation,
- Established intrauterine device (IUD) or intrauterine hormone releasing system (IUS).

- Bilateral tubal occlusion
- Vasectomy (A vasectomy is a highly effective contraception method provided the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used)
- Male is sterile due to a bilateral orchiectomy or radical cystoprostatectomy/removal of seminal vesicles
- Sexual Abstinence is considered a highly effective method only if defined as refraining from heterosexual activity during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant

[a] Local laws and regulations may require use of alternative and/or additional contraception methods.

12.4 List of Excluded Concomitant Medications

The following medications are prohibited within 4 weeks of day 1 and during the study treatment period:

- 5 α-reductase inhibitors (finasteride, dutasteride);
- Estrogens;
- Cyproterone acetate, megestrol acetate;
- Biologic or other agents with antitumor activity against prostate cancer (with the exception of those therapies identified in exclusion criterion No. 1);
- Systemic glucocorticoids greater than the equivalent of 10 mg/day of prednisone intended for the treatment of prostate cancer;
- Herbal medications with known hormonal antiprostate cancer activity and/or known to decrease PSA levels (i.e., saw palmetto);
- Androgens (testosterone, dehydroepiandrosterone, etc.);
- Investigational agents.

In addition, bisphosphonates and denosumab are prohibited unless stabilized for 2 weeks prior to randomization and held constant, as tolerated, throughout study treatment or administered for diagnosis of osteoporosis.

12.5 Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases to > 3 × ULN (to > 5 × ULN in subjects with liver metastases), or bilirubin > 2 × ULN, should undergo detailed testing for liver enzymes (including at least ALT, AST, alkaline phosphatase, and TBL). Testing should be repeated within 48 to 72 hours of notification of the test results. Moderate or severe liver abnormality should inform the investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

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

	ALT or AST		TBL
Moderate	> 3 × ULN (in subjects without liver metastases), > 5 × ULN (in subjects with liver metastases)	or	> 2 × ULN
Severe*	> 3 × ULN	and	> 2 × ULN

In addition, the subject 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 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 or 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. Subjects with confirmed abnormal LFTs 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 subject 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 subjects 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 eCRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis (NASH) is seen in obese hyperlipoproteinemic, and/or diabetic subjects and may be

associated with fluctuating aminotransferase levels. The investigator should ensure that the medical history form captures any illness that predates study enrollment that may be relevant in assessing hepatic function.

- Obtain a history of concomitant drug use (including nonprescription 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 subject'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, preexisting or acute liver disease, presence of liver metastases, or exposure to other agents associated with liver injury, the subject may be discontinued from the study. The investigator may determine that it is not in the subject'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 subjects 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 subjects 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 subject 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 × ULN elevations are too common in treated and untreated subjects

to be discriminating"). 2. Cases of increased bilirubin (at least 2 × ULN) with concurrent transaminase elevations at least 3 × ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's syndrome [Temple, 2006].

Reference

Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" issued by FDA on July 2009.

Temple R. Hy's law: predicting serious hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006 Apr;15(4):241-3.

12.6 Common Serious Adverse Events

The following is a list of SAEs that the sponsor considers to be associated with the disease state being studied. The list does **NOT** change the investigator's reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed in [Section 5.5.2 Definition of Serious Adverse Events]. The purpose of this list is to note that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common SAEs." The investigator is required to follow the requirements detailed in [Section 5.5.5 Reporting of Serious Adverse Events].

For IND safety reporting, single occurrences of the following events may be excluded from expedited reporting to the cFDA. If aggregate analysis of these events indicates they occur more frequently with study drug, an expedited IND safety report may be submitted to the cFDA.

- Anemia
- Anorexia
- Asthenia/Fatigue
- Bone pain
- Back pain
- Catheter-related infection
- Dyspnea
- Hematuria
- Hydronephrosis
- Metastases to bone
- Metastases to central nervous system
- Nausea
- Obstructive uropathy
- Pain

- Prostate cancer metastatic
- Renal failure
- Renal failure acute
- Spinal compression fracture
- Spinal cord compression
- Urinary retention
- Urinary tract infection
- Urinary tract obstruction
- Vomiting

12.7 ECOG Performance Status Scale

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

***Reference**

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

12.8 Soft Tissue Assessment (RECIST)

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Reproduced from: Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247.

12.9 Anti-Androgen Usage

Being a concomitant treatment, anti-androgen, i.e., flutamide, bicalutamide or nilutamide are permitted only if given concurrently with LHRH agonist (ADT medication) to prevent flare*. The treatment duration is allowed for 7 - 28 days.

Being a treatment in medical history, which means discontinuing before randomization (Day 1), anti- androgen, i.e., flutamide, bicalutamide or nilutamide are permitted in 2 scenarios:

- To prevent flare*, given concurrently with LHRH agonist. The treatment duration is allowed for 7 - 28 days.
- Given with or without ADT medication as a CAB regimen. The duration of ADT or anti-androgen usage from the date of first dosing, whichever is longer, shall be no longer than those criteria defined in exclusion criterion #1, i.e., 3 or 6 months prior to day 1 for subjects without/with docetaxel therapy.

* Suggest to record in source document the antiandrogen is utilized as “To prevent flare”.

12.10 Open-Label Phase

Before the sponsor's formal determination on study-wide unblinding, open-label enzalutamide will be supplied for free to the subjects in placebo arm who remain on study treatment until confirmed radiographic disease progression and in the judgement of the investigator who is necessary to initiate the next course of therapy till next disease progression based on subject's informed consent.

If the study results in a positive outcome and after the sponsor's formal determination on study-wide unblinding via written notice to study sites, open-label enzalutamide will be supplied for free to the subjects in both enzalutamide and placebo arms who remain on study treatment.

With the exception of those procedures and processes indicated below, this phase of the study will be performed using the same general approach as described in the protocol. Refer to the main protocol for any study details not contained in this supplemental open-label section.

12.10.1 Rationale

To maximize the treatment benefit and prolong the next disease progression to the subjects who are in the placebo arm remain on study treatment until confirmed radiographic disease progression, along with the judgement of the investigator it's necessary to initiate the next course of therapy and subject's informed consent, open-label enzalutamide will be provided.

Following the demonstration of a statistically significant advantage of enzalutamide over placebo when added to ADT and the sponsor's formal determination on study-wide unblinding, all eligible subjects on study could be treated with open-label enzalutamide at the discretion of the subject and investigator.

Day 1 of the open-label phase will occur after consent is signed and eligibility is confirmed. Treatment with open-label enzalutamide will be stopped when, in the opinion of the investigator, there is no added clinical benefit to continue treatment with enzalutamide, and/or when discontinuation criteria are met [Section 12.10.6 Duration of Treatment and Criteria for Discontinuation].

Subjects who do not participate in the open-label phase or who withdraw consent for further treatment will discontinue study treatment and return for a 30-day safety follow-up visit as per protocol. Long-term follow-up assessments will be completed as per protocol.

12.10.2 Schedule and Assessments

For procedures see Table 4 (Open-Label Phase Schedule of Assessments).

After being discontinued from the double-blind period and unblinding, subjects treated with placebo during the double-blind period will sign informed consent at the Open-Label screening visit after which they will be switched to enzalutamide in Open-Label Day 1(dosing below); these subjects will be required to return for study visits at Open-Label Week 5 (Day

29), Week 13 and every subsequent 12 weeks. Subjects treated with enzalutamide during the double-blind period will sign informed consent at the Open-Label screening visit and will continue receiving enzalutamide during the open-label phase; these subjects will be required to return for study visit every 12 weeks.

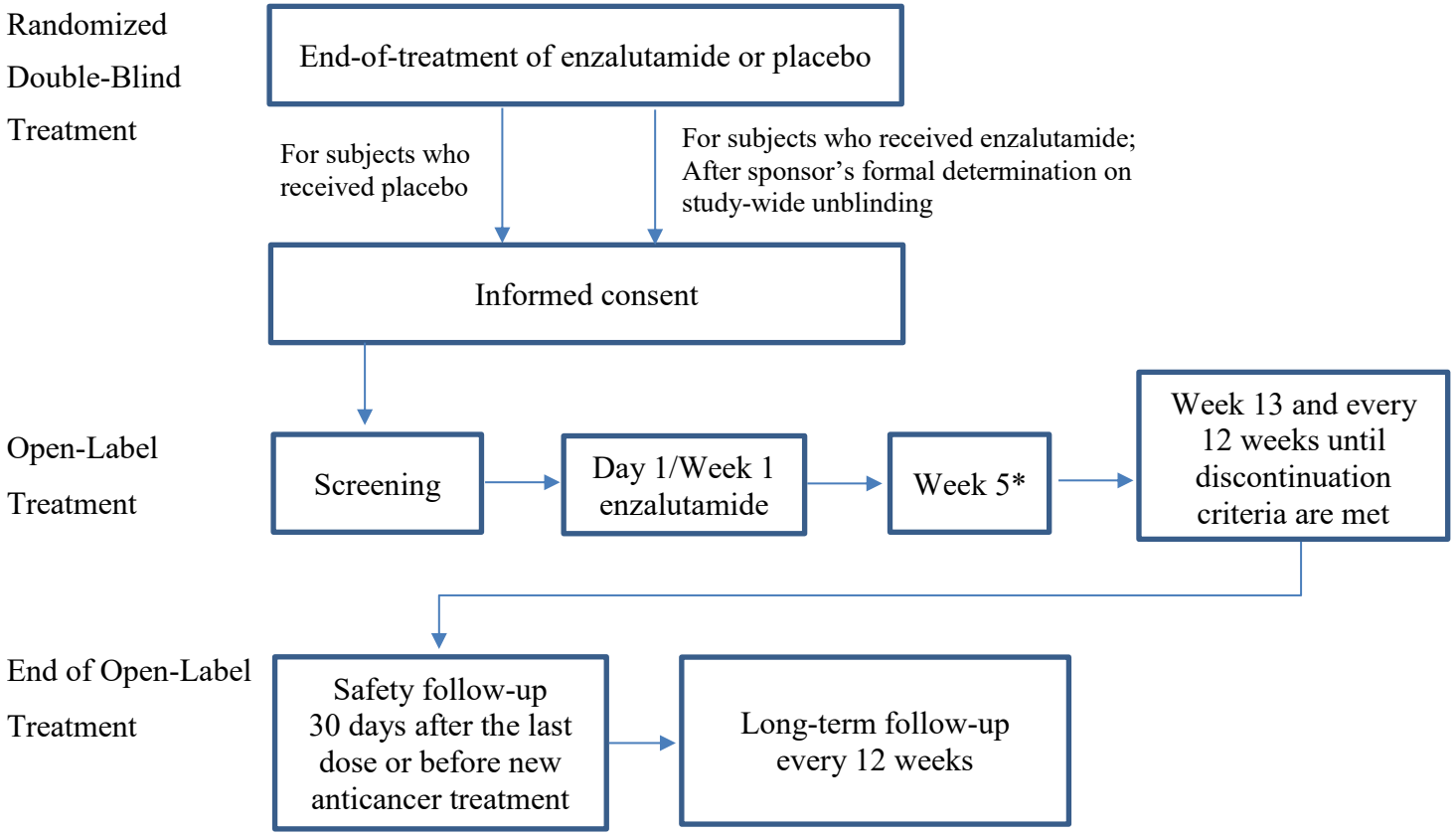
During the open-label phase, all subjects will take enzalutamide as four 40-mg soft gelatin capsules (160 mg/day) by mouth once daily with or without food, except that subjects who had a dose modification of enzalutamide during the double-blind period may continue at the current dose as appropriate. Dose modification is allowed during the open-label phase [Section 5.1.2 Increase or Reduction in Dose of the Study Drug(s)].

Study assessments will include safety evaluations including AEs, concomitant medications, clinical laboratory tests, brief physical examinations, ECGs and vital signs. During the open-label phase, for subjects who did not achieve radiographic disease progression, radiographic assessments (CT/MRI and bone scan) are recommended to be performed based on the investigator's discretion and clinical practice, but the data will not be collected in the study.

Subjects will have a safety follow-up 30 days after the last dose of open-label enzalutamide. If a new antineoplastic or investigational anticancer treatment is started before 30 days after the last dose of open-label enzalutamide, then safety follow-up should occur immediately before starting the new treatment.

Long-term follow-up data will be collected every 12 weeks. The information collected will include survival status, new antineoplastic therapies for prostate cancer, skeletal-related events and associated interventions.

Flow Chart – Open-Label Phase



* Week 5 visit is only required for subjects previously receiving placebo.

12.10.3 Inclusion Criteria

The inclusion criteria apply to subjects receiving enzalutamide or placebo during double-blind treatment. Eligible subjects must meet all inclusion criteria below:

1. Before the sponsor's formal determination on study-wide unblinding, includes the subject who has evidence of radiographic progression as confirmed during the double-blind treatment (only apply to the subject in the placebo arm).
2. Subject has not met any of the discontinuation criteria in the main protocol [Section 6 Discontinuation]. Subject in the placebo arm who achieved confirmed radiographic progression in the double-blinded period is eligible.
3. Subject is willing to maintain ADT with LHRH agonist or antagonist or has had a bilateral orchiectomy.
4. Subject is able to swallow enzalutamide capsules whole and to comply with study requirements throughout the study.
5. Subject and subject's female partner agree to follow contraception and sperm donation requirements in main protocol [Section 3.2 Inclusion Criteria].
6. IRB-/IEC-approved written informed consent and privacy language as per national regulations must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
7. Subject is considered an adult according to local regulation at the time of signing informed consent.
8. After the sponsor's formal determination on study-wide unblinding, includes the subject who is randomized to receive treatment in the double-blind period (apply to all subjects).

12.10.4 Exclusion Criteria

Subjects will be excluded from participation if any of the following apply:

1. Subject has taken commercially available enzalutamide (Xtandi).
2. After unblinding, subject has started any new investigational agent or anti-neoplastic therapy intended to treat prostate cancer.
3. Subject has any clinically significant disorder or condition including excessive alcohol or drug abuse, or secondary malignancy, which may interfere with study participation in the opinion of the investigator or medical monitor.
4. Subject has current or previously treated brain metastasis or active leptomeningeal disease.
5. Subject has a history of seizure or any condition that may increase the risk of seizure.
6. Subject's disease has progressed radiographically during the double-blind period of the study and treatment with study drug was stopped prior to study-wide unblinding. (Note:

Subject who progressed radiographically while in the double-blind period of the study and continued treatment per protocol is allowed to participate in the open-label phase.)

12.10.5 Enzalutamide Administration, Storage and Accountability

All subjects will self-administer four 40-mg soft gelatin enzalutamide capsules (160 mg/day) by mouth once daily with or without food, any dose modification must consult and confirm with assigned site investigator, and refer to [Section 5.1.2 Increase or Reduction in Dose of the Study Drug(s)] for dose modification instructions. Subjects should return all enzalutamide bottles, including unused enzalutamide to the site at each visit.

Enzalutamide should be handled and stored safely and properly in accordance with the bottle label. Study site personnel must make all reasonable efforts to obtain all bottles and unused enzalutamide from subjects who do not routinely return the bottles at study site visits.

12.10.6 Duration of Treatment and Criteria for Discontinuation

Open-label enzalutamide administration may continue as long as the investigator considers treatment to be beneficial or until any of the following discontinuation criteria are met:

- Any AE that is intolerable to the subject and which cannot be ameliorated by adequate medical intervention and/or dose reduction or that in the opinion of the investigator or medical monitor would lead to undue risk if enzalutamide continues.
- Seizure or any condition that significantly predisposes the subject to seizure such as brain metastasis or clinically evident stroke.
- Confirmed event of PRES by brain imaging, preferably MRI.
- Initiation of investigational agent or new therapy for prostate cancer.
- Gross noncompliance with protocol procedures and/or enzalutamide study drug management.
- Withdrawal of consent by subject for any reason. Subject may withdraw consent for further treatment with enzalutamide study drug, but may still participate in the long-term follow-up assessments. Specific details of procedures declined or allowed should be documented by study staff.
- Subject is lost to follow-up despite reasonable efforts by the investigator to contact subject to complete study related assessments, record outstanding data and retrieve enzalutamide study drug. Following unsuccessful telephone contact, an effort should be made to contact the subject by mail using a method that provides proof of receipt. Alternate contacts are permissible if subject is not reachable and allowed by local guidelines.
- Study termination by sponsor.
- Death.

Subject will be discontinued from the open-label phase follow-up (Safety or Long term Follow-up) if any of the following occur:

- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Subject withdraws consent for further follow-up.
- Death.
- Study termination by the Sponsor.

12.10.7 Statistical Methods

Data collected in the open-label phase will be summarized by descriptive statistics for subjects started open-label enzalutamide in the open-label phase before the study-wide unblinding, and as needed and appropriate for all subjects who received open-label enzalutamide after study-wide unblinding, unless otherwise specified. The details will be provided in the applicable SAPs. The subjects who start open-label enzalutamide before the study-wide unblinding are post-radiographic progression.

Subject disposition data (subjects who continued to the open-label phase and primary reasons for treatment discontinuation and study discontinuation) will be summarized descriptively in the ITT population for subjects who started open-label enzalutamide for the open-label phase, as needed and appropriate.

Safety data will be summarized for subjects receiving open-label enzalutamide as applicable.

Enzalutamide exposure will be summarized and listed in the open-label phase, as needed and appropriate.

Adverse events will be coded using MedDRA. The number and percentage of AEs, SAEs, AEs leading to discontinuation and AEs related to study drug will be summarized by system organ class and preferred term. The number and percentage of AEs by severity (reported according to NCI-CTCAE version 4.03) will also be summarized. All AEs will be listed.

For quantitative laboratory measurements and vital signs, descriptive statistics will be used to summarize results and change from baseline by visit. Baseline will be defined as the latest value recorded prior to the first enzalutamide administration. Using the NCI-CTCAE version 4.03, laboratory values will be classified as Grade 1 through 4, where possible. Laboratory and vital sign data will be displayed in listings.

Table 4 Open-Label Phase Schedule of Assessments

Study Period or Visit	**OL Screening**	**OL Treatment**			**Unscheduled Visit**	**OL Safety Follow-up**	**OL Long Term Follow-up**
Study Week	**NA**	**OL 1[1] (Day 1)**	**OL 5[2] (Day 29)**	**OL 13 and Every Subsequent 12 Weeks (Day 85 and Every Subsequent 84 Days)**	**Varies[3]**	**30 Days after Last Dose[4]**	**Every 12 Weeks**
Window (Days)	NA	NA	± 3	± 5	NA	± 7	± 7
Informed Consent[5]	X						
Inclusion/Exclusion Criteria	X						
Open-Label Enrollment		X					
Brief Physical Examination		X		X	X	X	
Vital Signs including Weight		X	X	X	X	X	
ECOG Performance Status		X	X	X	X	X	
12-lead Electrocardiogram		X				X	
Clinical Labs[6]		X	X	X	X	X	
Adverse Events[7]		X	X	X	X	X	
Concomitant Medication Review		X	X	X	X	X	
Study Drug Dispensing		X	X	X			
Study Drug Accountability		X	X	X		X	
Long-Term Follow-up Assessments[8]							X

ECOG: Eastern Cooperative Oncology Group; OL: Open-Label.

With the exception of those procedures and processes indicated below, this phase of the study will be performed using the same general approach as described in the protocol.

At OL1 Visit, the following assessments (ECG; vital signs; physical examination; clinical labs; ECOG) do not need to be repeated if they were completed within 7 days in Safety Follow-up Visit during double-blind period.

1 All the assessments in OL 1 Visit should be performed before treatment. The OL 1 Visit and the Safety Follow-up Visit for the double-blind period can be combined.

2 Only for subjects who received placebo in the double-blind period.

3 As necessary to assess or follow up adverse events.

4 Prior to initiation of new antineoplastic therapy for prostate cancer, or 30 days after last dose of enzalutamide, whichever occurs first.

5 Informed consent must be obtained during screening before performing any study-specific procedures for all subjects participating in OL phase.

6 Laboratory assessments include serum chemistries and hematology.

7 Adverse events collection begins after the signing of the informed consent for the double-blind period and will be collected until 30 days after the last dose of study drug (including the double-blind period and open-label phase if applicable), or initiation of a new therapy for prostate cancer, or the subject is determined to be a screen failure, whichever occurs first. During the post treatment follow-up period, only symptomatic skeletal events need to be reported.

8 Long-term follow-up assessments include survival status, symptomatic skeletal events and new antineoplastic therapies for prostate cancer. May be obtained by telephone contact, chart review or clinic visit.

12.11 Clinical Study Continuity

INTRODUCTION

The purpose of this appendix is to provide acceptable alternate methods to assess safety and efficacy parameters, as appropriate, in the event the clinical study is interrupted at the country, state, site or participant level during any crisis (e.g., natural disaster, pandemic).

BENEFIT-RISK RATIONALE

Maintaining the safety of clinical study participants and delivering continuity of care in the clinical study setting is paramount during any crisis. The site is expected to follow the protocol and associated Schedule of Assessments [Table 1] unless the site investigator discusses the need with the Astellas medical monitor or designee to implement the alternate measures.

The approach outlined within this appendix defines which assessments are required to maintain a favorable benefit/risk to the participant, to maintain overall study integrity and to provide acceptable alternate methods to complete the study required assessments and procedures if study activities are unable to be performed as described in [Section 5] due to a crisis.

INFORMED CONSENT

Participants who need to follow any or all of the alternate measures outlined in this Appendix will be required to provide informed consent, which explicitly informs them of the nature of and rationale for these changes, and gain their agreement to continue participation in the study prior to the implementation of any of these changes. In the event the urgency of implementing the alternate measures does not allow for the participant to provide written consent prior to implementation, the investigator or designee will obtain oral agreement from the subject followed by written documentation as soon as is feasible.

PARTICIPANT PROCEDURES ASSESSMENT

Sites with participants who are currently enrolled into this clinical study may consider implementing the alternate methods outlined below if one or more of the following conditions are met due to the crisis:

- Regional or local travel has been restricted, inclusive of mandatory shelter in place measures, which makes participant travel to/from the study site nearly impossible.
- Site facilities have been closed for clinical study conduct.
- Site has been restricted to treating patients with conditions outside of the scope of the study.
- Site personnel have temporarily relocated the conduct of the study to a location that place a burden on the participant with respect to time and travel.
- Participant(s) have temporarily relocated from the current study site to an alternate study site to avoid placing a burden on the participant with respect to travel.
- Participant(s) have temporarily relocated from their home location and the new distances from the site would cause undue burden with respect to time and travel.

- Participant has risk factors for which traveling to the site poses an additional risk to the participant's health and safety.

Adherence to the original protocol as reflected in the Schedule of Assessments [Table 1] is expected, where plausible, in the case of a crisis. The alternate measures as noted below are only permissible in the event of a crisis, and after discussing the need with the Astellas medical monitor or designee to implement the alternate measures.

- Remote visit by the investigator is recommended to assess AE and review concomitant medications for subject who cannot have on-site visit(s) due to the crisis. Subjects are suggested to undergo necessary examinations such as laboratory tests and imaging assessments in local hospitals. Examination results from a local hospital could be used to assess the subject's related conditions and safety situation. All the data collected by remote visits and local hospitals, such as laboratory reports, medical records by the physicians at local hospitals, AEs/SAEs/other safety information, should be submitted to the investigators and study sites promptly to support safety evaluation per protocol. In addition, these data should be filed and/or recorded in the source documents.
- If a subject had remote visits for 3 or more consecutive months without any laboratory test results to support safety evaluation, the investigator should evaluate the suitability of the subject to continue the study.
- If a subject cannot have on-site visits, the study drug can be shipped to subject's residence via courier (temperature-controlled if possible) to ensure the treatment can be continued.

This is to allow for continuity of receiving study drug and maintaining critical safety and efficacy assessments for participants in the study at a time of crisis.

If one or more of the alternate measures noted above is implemented for a participant, the site should document in the participant's source document the justification for implementing the alternate measure and the actual alternate measures that were implemented, along with the corresponding time point(s).

STUDY DRUG SUPPLY

If any of the conditions outlined above in the Participants Procedures Assessment are met, one or all of the following mitigating strategies will be employed, as needed, to ensure continuity of study drug supply to the participants:

- Increase stock of study drug on site to reduce number of shipments required, if site space will allow.
- Direct-to-Participant (DTP) shipments of study drug from the site to the participant's home.

DATA COLLECTION REQUIREMENTS

Additional data may be collected in order to indicate how participation in the study may have been affected by a crisis and to accommodate data collection resulting from alternate measures implemented to manage the conduct of the study and participant safety.

- Critical assessments for safety and efficacy based on study endpoints to be identified as missing or altered (performed virtually, at alternative locations, out of window or other modifications) due to the crisis.

13 SPONSOR'S SIGNATURES

Astellas Signatories

(Electronic signatures are attached at the end of the document)