

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

ISN/Protocol 9785-CL-0335

Version 5.1

Incorporating Nonsubstantial Amendment 6 [See [Section 13](#)]

18 Apr 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 14, Signatures](#)]; e-signatures (when applicable) are located at the end of this document.

2. INVESTIGATOR'S SIGNATURE

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

ISN/Protocol 9785-CL-0335

Version 5.1 Incorporating Nonsubstantial Amendment 6

18 Apr 2022

I have read all pages of this clinical study protocol for which Astellas is the sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines and applicable local regulations. I will also ensure that 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

<p>24-hour Contact for Serious Adverse Events (SAEs)</p> <p>See [Section 5.5.5]</p>	<p><i>PPD</i> <i>PPD</i>, Development Medical Science - Oncology Astellas Pharma Global Development, Inc.</p> <p><i>PPD</i></p> <p>Fax the SAE Worksheet to: Astellas Pharma Global Development, Inc Pharmacovigilance North America Fax number: 1-888-396-3750 North America Alternate Fax: 1-847-317-1241 International Fax: +44 800 471 5263 Email: safety-us@astellas.com</p> <p>Specific to sites in Japan: Japan/Asia Clinical Development 1, Development Astellas Pharma, Inc Phone: 03-3244-1222 Fax: 03-3243-5737</p>
<p>Medical Monitor/Medical Expert:</p>	<p><i>PPD</i> <i>PPD</i>, Development Medical Science - Oncology Astellas Pharma Global Development, Inc.</p> <p><i>PPD</i></p> <p><i>PPD</i></p> <p>Astellas Pharma Global Development, Inc.</p> <p><i>PPD</i></p>
<p>Clinical Research Contacts:</p>	<p><i>PPD</i></p>

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
ADT	Androgen deprivation therapy
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
APEBV	Astellas Pharma Europe B.V.
APGD	Astellas Pharma Global Development, Inc
AR	Androgen receptor
AST	Aspartate aminotransferase
AUST	Astellas United States Technologies, Inc
BHA	Butylated hydroxyanisole
BHT	Butylated hydroxytoluene
BPI-SF	Brief Pain Inventory-Short Form
CIOMS	Council for International Organizations of Medical Sciences
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
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EQ-5D-5L	EuroQol Group-5 Dimension-5 Level Instrument
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
ICF	Informed consent form
ICH	International Council on Harmonisation

Abbreviations	Description of abbreviations
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISN	International study number
ITT	Intent-to-treat
KRAS	Kirsten rat sarcoma viral oncogene homolog
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
MedDRA	Medical Dictionary for Regulatory Activities
mHSPC	Metastatic hormone sensitive prostate cancer
MRI	Magnetic resonance imaging
NASH	Nonalcoholic steatohepatitis
NCI	National Cancer Institute
NRAS	Neuroblastoma RAS viral oncogene homolog
NSAA	Nonsteroidal antiandrogen
ORR	Objective response rate
OS	Overall survival
P-gp	P-glycoprotein
PIK3CA	Phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit alpha
PGx	Pharmacogenomics
PRES	Posterior reversible encephalopathy syndrome
PSA	Prostate-specific antigen
PSADecR	Rate of PSA decline to < 0.2ng/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

Abbreviations	Description of abbreviations
TBL	Total bilirubin
TTNAnti	Time to initiation of a new antineoplastic therapy
TTPSA	Time to PSA progression
TTUri	Time to deterioration in urinary symptoms
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.
Study period	Period of time from the first site initiation date to the last site completing the study.

IV. SYNOPSIS

Date and Version # of Protocol Synopsis:	18 Apr 2022, Version 5.1
Sponsor: Astellas Pharma Global Development, Inc (APGD)	Protocol Number: 9785-CL-0335
Name of Study Drug: Enzalutamide	Phase of Development: Phase 3
Title of Study: ARCHES: A Multinational, Phase 3, Randomized, Double-blind, Placebo-controlled Efficacy and Safety Study of Enzalutamide Plus Androgen Deprivation Therapy (ADT) Versus Placebo Plus ADT in Patients with Metastatic Hormone Sensitive Prostate Cancer (mHSPC)	
Planned Study Period: 1Q2016 to 1Q2024	
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 subjects with metastatic hormone sensitive prostate cancer (mHSPC). <u>Primary Objective</u> <ul style="list-style-type: none"> To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by radiographic progression-free survival (rPFS) based on central review <u>Secondary Objectives</u> <ul style="list-style-type: none"> To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by overall survival (OS) 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 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]), in particular by: <ul style="list-style-type: none"> time to deterioration in urinary symptoms using a modified urinary symptoms scale from QLQ-PR25 time to deterioration in QoL using the FACT-P global score 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 time to prostate-specific antigen (PSA) progression 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) 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]) <u>Safety Objective</u> <ul style="list-style-type: none"> To determine the safety of enzalutamide plus ADT as compared to placebo plus ADT 	

Exploratory Objective (North America sites only)

- To determine gene mutations potentially related to resistance of enzalutamide plus ADT as assessed by DNA mutation testing in plasma

Planned Total Number of Study Centers and Location(s):

Approximately 250 centers globally

Study Population:

The study population will consist of subjects with mHSPC.

Number of Subjects to be Randomized:

Approximately 1100 subjects

Study Design Overview:

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

Approximately 1100 subjects will be randomized centrally 1:1, and the randomization will be stratified by volume of disease (low versus high) and prior docetaxel therapy for prostate cancer (no prior docetaxel, 1-5 cycles, 6 cycles). 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.

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 an investigational agent or new therapy for treatment of prostate cancer. It is recommended that subjects remain on study treatment until radiographic progression is confirmed by independent central imaging review. Subjects who discontinue study treatment without radiographic progression will continue to follow the radiographic assessment schedule until radiographic progression event is confirmed by the central imaging independent reviewer or until the target number of progression events is reached as assessed by the central review. All subjects will be followed until death to assess for OS. Once the final number of events has been reached to trigger the final OS analysis, survival follow-up will be considered complete and subjects will be discontinued from long term follow-up.

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 for independent central review. 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

Table continued on next page

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 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.

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. Once the final number of events has been reached to trigger the final OS analysis, sites will no longer be required to collect EQ-5D-5L, QLQ-PR25, FACT-P for QoL and BPI-SF.

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.

An independent Data Safety Monitoring Board (DSMB) will monitor the safety data on an ongoing basis.

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. All subjects are to be followed for survival until death, loss to follow-up, withdrawal of consent, final OS analysis or study termination by the Sponsor. Once a sufficient number of death events has been reached for the OS analysis, survival follow-up will be considered complete and the long term follow-up process and QoL assessments collection will discontinue for all study participants.

Subjects who are continuing to receive clinical benefit from treatment with enzalutamide after the OS analysis data cutoff or at study termination and have not met any discontinuation criteria may continue their open-label treatment in another Astellas-sponsored study.

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 data gathered from the ARCHES study may be used to support future research studies.

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 (e.g., Health Insurance Portability Accountability Act authorization for United States sites) 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. Specific to subjects enrolled in France, histological diagnosis is required.
4. Subject has metastatic prostate cancer documented by positive bone scan (for bone disease) or 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 a luteinizing hormone-releasing hormone (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 and his female partner who is of childbearing potential must use 2 acceptable methods of birth control (1 of which must include a condom as a barrier method of contraception) from screening through 3 months after the last dose of study drug. Two acceptable methods of birth control include condom (barrier method is required) AND 1 of the following:
 - Consistent and correct usage of established, proper use of hormonal contraceptives that inhibit ovulation by the female partner;
 - Established intrauterine device or intrauterine system by the female partner;
 - Tubal ligation in the female partner performed at least 6 months prior to subject's screening visit;
 - Vasectomy or other procedure resulting in infertility (e.g., bilateral orchiectomy) performed at least 6 months prior to screening;
 - Calendar-based contraceptive methods (Knaus-Ogino or rhythm method applicable to subjects enrolled in Japan only).
10. Subject must use a condom throughout the study if engaging in sexual intercourse with a pregnant woman.
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 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 antiproliferative 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/ μ L, platelet count < 100000/ μ L 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 \geq 1.5 x the upper limit of normal (except subjects with documented Gilbert's disease), or alanine aminotransferase or aspartate aminotransferase \geq 2.5 x the upper limit of normal at screening.
 13. Subject has creatinine > 2 mg/dL (177 μ mol/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 \geq 45%;
 - History of clinically significant ventricular arrhythmias (e.g., sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes);

<ul style="list-style-type: none"> 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. <p>18. Subject has gastrointestinal disorder affecting absorption.</p> <p>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.</p> <p>20. Subject received bisphosphonates or denosumab within 2 weeks prior to day 1 unless administered at stable dose or to treat diagnosed osteoporosis.</p> <p>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).</p> <p>Waivers to the exclusion criteria will NOT be allowed.</p>
<p>Investigational Product(s): Enzalutamide 40 mg capsule</p> <p>Dose(s): 160 mg once daily</p>
<p>Mode of Administration: Oral, with or without food</p>
<p>Comparative Drug(s): Placebo capsules that are identical in appearance to enzalutamide will be administered in the same manner and frequency as enzalutamide.</p>
<p>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.</p>
<p>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.</p>

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;
- Biologic or other agents with potential 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 antiprostata 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.

Duration of Treatment:

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

Subjects may be asked to continue their open-label treatment in another Astellas-sponsored study.

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 an investigational agent or new therapy for prostate cancer.
- Subject who has evidence of radiological disease progression as confirmed by the independent reader 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) as confirmed by the central laboratory.
- 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.
- Final analysis for OS completed.
- Study termination by the Sponsor.

Formal Stopping Rules:

Not applicable

Endpoints for Evaluation:

Primary Endpoints

- rPFS (based on central review)

Secondary Endpoints

- OS
- Time to first SSE
- Time to castration resistance
- Time to deterioration of QoL
- Time to deterioration in urinary symptoms
- Time to initiation of new antineoplastic therapy
- Time to PSA progression (≥ 2 ng/mL) (Prostate Cancer Clinical Trials Working Group 2 criteria)
- PSA undetectable rate (< 0.2 ng/mL)
- ORR
- 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)

Exploratory Endpoint (North America sites only)

- Mutation status in plasma of genes potentially related to resistance of enzalutamide plus ADT

Statistical Methods:

Sample Size Justification:

Approximately 1100 subjects (550 subjects per treatment arm) will be randomized in the study.

The final analysis of rPFS will be conducted with a minimum of 262 progression events based on the following considerations:

A target hazard ratio (HR) is 0.67. The expected median rPFS for the ADT arm is 20 months as measured from the date of randomization. A target HR of 0.67 corresponds to approximately 50% increase in median rPFS for the enzalutamide plus ADT arm relative to the placebo plus ADT arm (approximately 30 versus 20 months).

The required minimum of 262 rPFS events (radiographic progression or death on study, defined as death from any cause within 24 weeks after treatment discontinuation, whichever occurs first) provides 90% power to detect a target HR of 0.67 based on a 2-sided log-rank test and significance level of 0.05.

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

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

Secondary Endpoints

- *OS*: Defined as the time from randomization to death from any cause.
- *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.
- *Time to deterioration of QoL*: Defined as time from randomization to a 10-point reduction of the FACT-P total score.
- *Time to deterioration in urinary symptoms*: Defined as time from randomization to an increase of $\geq 50\%$ of the standard deviation at baseline in the modified urinary symptoms score of QoL PR25.
- *Time to initiation of a new antineoplastic therapy*: Defined as the time from randomization to the initiation of antineoplastic subsequent to the study treatments.
- *Time to PSA progression*: Defined as the time from randomization to PSA progression, which is a $\geq 25\%$ increase and an absolute increase of $\geq 2 \mu\text{g/L}$ (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.
- *PSA undetectable rate*: Defined as percentage of subjects with detectable ($\geq 0.2 \text{ ng/mL}$) PSA at baseline which become undetectable ($< 0.2 \text{ ng/mL}$) 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.
- *Time to pain progression*: Defined as time from randomization to an increase of $\geq 30\%$ in pain severity score from baseline using the BPI-SF.

All secondary endpoint analyses will be performed at the time of the rPFS primary analysis.

Six secondary endpoints (OS, time to PSA progression, time to initiation of a new antineoplastic therapy, the rate of PSA decline to $< 0.2 \text{ ng/mL}$, ORR and time to deterioration in urinary symptoms) will be tested utilizing a parallel testing strategy. The methodology used will be described in detail in the statistical analysis plan.

Time to event endpoints such as rPFS, time to PSA progression, OS, time to first SSE, time to castration resistance, time to deterioration of QoL, time to deterioration in urinary symptoms, 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 will be used to estimate the HR and the associated 95% CI. The median will be estimated using the Kaplan-Meier method.

One interim analysis and the final analysis are planned for OS. The interim analysis of OS will be performed at the time of the rPFS final analysis. The significance level will be determined by the O'Brien-Fleming alpha spending function based on the number of events observed at the interim look. The final analysis of OS will be conducted when approximately 342 deaths are observed to ensure an adequate number of events for the evaluation of OS.

The proportion endpoints such as 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.

Exploratory:

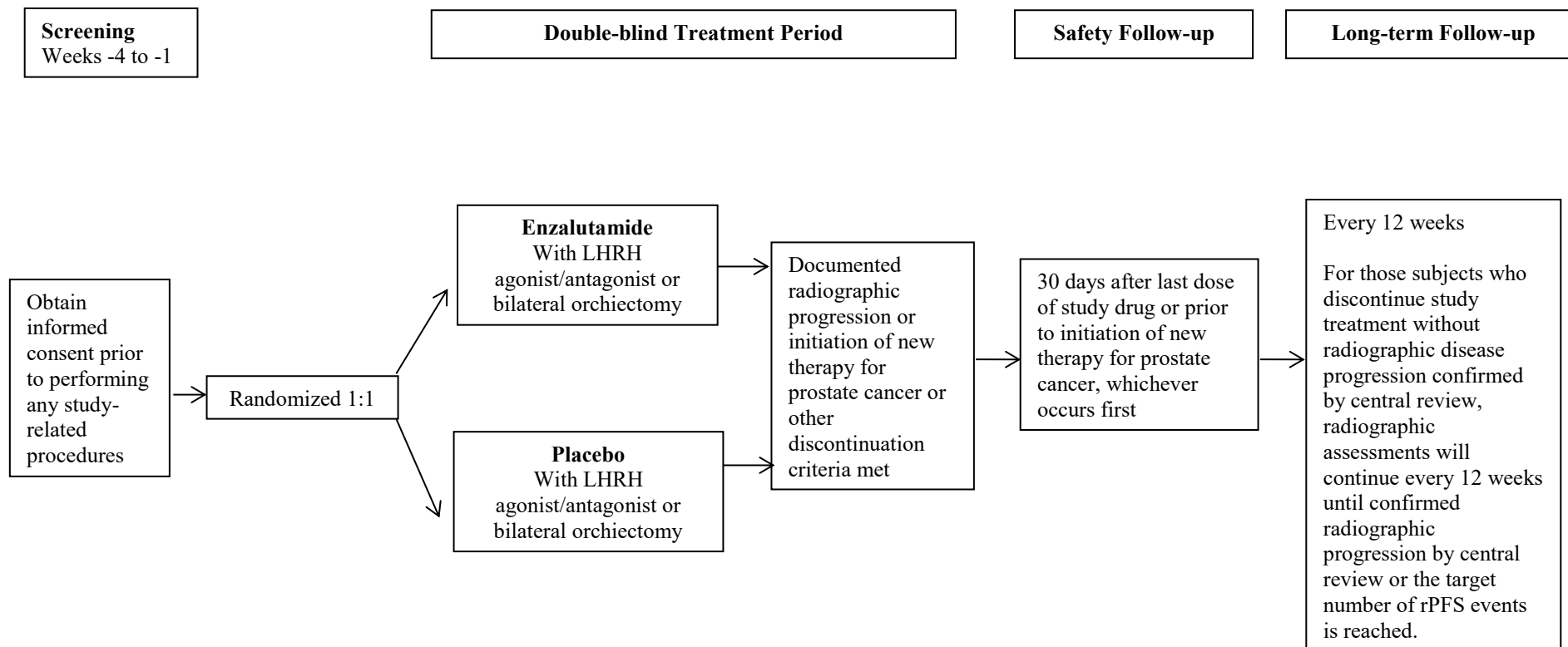
Mutations status will be summarized by descriptive statistics, including number of subjects, variant frequency, mean, standard deviation, minimum, median and maximum, and individual mutation status over time will be evaluated for samples collected in North America.

Interim Analysis:

No formal interim analysis is planned for rPFS. One interim analysis of OS will be performed at the time of the rPFS final analysis. If this interim analysis of OS is statistically significant, it will be reported as the final analysis and no subsequent analysis will be performed.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart



LHRH: luteinizing hormone-releasing hormone; rPFS: radiographic progression-free survival

Table 1 Schedule of Assessments

Study Day	Screening Visit	1	29	85 and Every Subsequent 84 Days	Safety Follow-up	Unscheduled Visit†	Long Term Follow-up‡
Study Week	-4 to -1 (28 Days)	1	5	13 and Every Subsequent 12 Weeks	30 Days after Last Dose§		Every 12 Weeks
Window (Days)			± 5	± 5	± 7	NA	± 7
Informed Consent	X						
Medical History	X						
Inclusion/Exclusion Criteria	X	X					
Randomization (IRT)		X					
Vital Signs	X	X	X	X	X	X	
Physical Examination including Weight¶	X	X	X	X	X	X	
Height	X						
12-lead ECG	X	X			X		
Clinical Labs††	X	X	X	X	X	X	
PSA	X	X	X	X	X		
Sample for Genotyping Analysis‡‡		X					
Sample for Mutation Analysis§§		X		X			
Testosterone				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‡
Adverse Events§§§	X	X	X	X	X	X	
Previous and Concomitant Medications	X	X	X	X	X	X	
Study Drug Dispensing		X	X	X			
Study Drug Treatment		X	X	X			

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

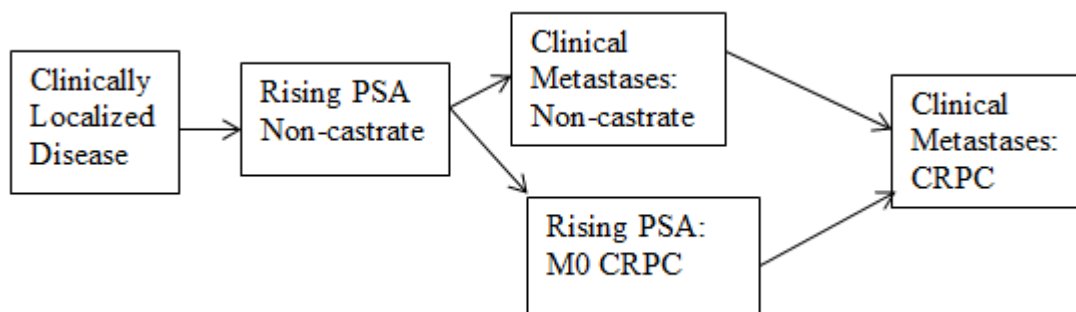
Footnotes continued on next page

- † 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. Testosterone testing through central laboratory at unscheduled visit requires prior sponsor approval.
- ‡ After treatment discontinuation, all subjects MUST undergo long term follow-up. Long term follow-up assessments will include monitoring for survival status, new antineoplastic therapies for prostate cancer and symptomatic skeletal events. Follow-up may be conducted by telephone interview. Subjects will continue to be scanned every 12 weeks until radiographic progression is confirmed by independent review or the number of rPFS events is reached. For subjects continuing with radiological assessments, if seen in clinic, QoL assessment will also be completed until the initiation of new antineoplastic therapy for prostate cancer or the number of progression events is reached. Additional follow-up contacts may be requested. Subjects will be followed for OS until death, lost to follow up, final OS analysis or termination of the study by the sponsor. When the final number of events has been reached to trigger the final OS analysis, QoL assessments will no longer be collected.
- § Or prior to initiation of 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.
- ‡‡ Genotyping samples will only be collected from subjects who agree to provide genotyping samples as documented by signing a separate genotyping informed consent form.
- || For sites in North America only: Blood samples for mutation analysis will be collected from subjects who agree to provide samples as documented by signing a separate genotyping informed consent form. Samples will be collected at randomization, at week 49 and at study treatment discontinuation.
- §§ The abdominal-pelvic CT scan or MRI, bone scan, chest x-ray or chest 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-designated independent central review facility.
- ¶¶ The window for all radiological (CT/MRI) assessments is ± 7 days. For subjects who discontinue study treatment without radiographic progression confirmed by central review, subjects will continue to be scanned every 12 weeks until radiographic progression is confirmed by independent review or the number of rPFS events is reached.
- ††† Chest CT/MRI is required at all imaging time points if screening chest x-ray demonstrates metastatic chest disease.
- §§§ Adverse events will be collected from the time the subject signs the consent form until the end of the safety reporting period (or until screen failure). The safety reporting period ends at the time of the safety follow-up visit, 30 days after last dose of study drug or initiation of new antineoplastic therapy for prostate cancer.

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].

Figure 1 Clinical States Model of Prostate Cancer Progression



CRPC: castration-resistant prostate cancer; PSA: prostate-specific antigen; M0: nonmetastatic

Source: modified from [Scher & 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 flashes, 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 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.

More effective therapies for subjects with mHSPC are needed because a proportion of mHSPC subjects treated with current therapies still develop castration-resistant prostate cancer (CRPC) relatively quickly and suffer from disease-related morbidity and mortality. This study is designed to determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT in subjects with mHSPC.

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 and prolong OS. As such, this study aims to determine whether enzalutamide with its superior ability of androgen suppression will improve radiographic progression-free survival (rPFS) 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 ($AUC_{24h} \approx 317 \mu g \cdot h/mL$), which resulted in plasma exposure levels similar to the clinical exposure ($AUC_{24h} 322 \mu g \cdot h/mL$) 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. 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 (Section 5.3, Company Core Data Sheet version 6.0).

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 (studies PRO3100NC39, PRO3100NC18 and PRO3100NC38 referenced in Company Core Data Sheet version 6.0). 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 (study 9785-ME-0046 referenced in Company Core Data Sheet version 6.0). 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 the data cutoff date of 30 Aug 2019, over 9000 subjects with prostate cancer, over 300 women with breast cancer, and over 300 subjects with no known cancer including healthy male subjects and subjects with hepatic impairment have received at least 1 dose of enzalutamide in completed and ongoing clinical studies (not including the expanded access program or 2 compassionate use programs).

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 [$\text{CLCR} \geq 30 \text{ mL/minute}$]) 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 ($\text{CLCR} < 30 \text{ mL/minute}$) and end-stage renal disease on enzalutamide pharmacokinetics.

A clinical drug-drug interaction study 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).

Another clinical drug-drug interaction study 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 starting 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 starting 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

Enzalutamide has been approved by the FDA, the EMA and Japan MHLW for metastatic CRPC. Worldwide, enzalutamide has been approved for the treatment of metastatic CRPC in more than 100 countries. Enzalutamide has also been approved for nonmetastatic CRPC in the US, EU and Japan as well as in more than 60 countries. In Dec 2019, enzalutamide was approved for the treatment of metastatic CSPC in the US (also referred to as mHSPC) and a marketing application for this indication is currently in review in the EU.

The safety profile of enzalutamide in subjects with CRPC is derived primarily from 5 phase 3 studies. Study CRPC2 (AFFIRM) was a randomized, double-blind, placebo-controlled, efficacy and safety clinical study of enzalutamide (160 mg daily) in 1199 subjects with progressive metastatic CRPC (mCRPC) previously treated with docetaxel-based chemotherapy. Study MDV3100-03 (PREVAIL) was a multinational, randomized, double-blind, placebo-controlled, efficacy and safety clinical study of enzalutamide in 1717 chemotherapy naïve subjects with mCRPC who have failed ADT. Study 9785-CL-0232 (Asian PREVAIL) was similar to PREVAIL except in an Asian population of 388 subjects. Study MDV3100-14 (PROSPER) was a randomized, double-blind, placebo-controlled, efficacy and safety clinical study of enzalutamide (160 mg daily) in 1401 subjects with nonmetastatic CRPC at high risk of disease progression based on baseline prostate-specific antigen (PSA) level and short PSA doubling time.

An analysis of 5 pooled phase 3 studies (AFFIRM, PREVAIL, Asian PREVAIL, PROSPER and ARCHES) indicated that the most frequently reported treatment-emergent adverse events (TEAEs) reported in $\geq 10\%$ of patients in the enzalutamide group ($n = 3371$; enzalutamide dose; 160 mg/day) were: fatigue, back pain, nausea, hot flush, constipation, arthralgia, decreased appetite, diarrhea, hypertension, asthenia, fall, pain in extremity, musculoskeletal pain and headache. With the exception of nausea and pain in extremity, each of these events occurred in the pooled phase 3 enzalutamide group with a $\geq 2\%$ higher incidence than in the placebo group ($n = 2472$). Only 2 TEAEs showed a higher rate in the enzalutamide vs the placebo group (event rate per 100 patient-years of treatment): fall (8.9% enzalutamide vs 4.6% placebo) and hypertension (8.2% vs 5.5%).

When adjusted for treatment duration, the event rates for grade ≥ 3 TEAEs showed small differences (≤ 1.2 events per 100 patient years) between the enzalutamide group and the placebo group.

Study drug-related TEAEs reported in $\geq 5\%$ of patients in the enzalutamide group were fatigue (24.1% enzalutamide vs 14.1% placebo), hot flush (14.0% vs 8.7%), nausea (11.7% vs 10.4%), decreased appetite (8.2% vs 5.5%), asthenia (7.4% vs 4.4%), diarrhea (5.6% vs 4.4%) and hypertension (5.6% vs 2.0%).

The incidence of TEAEs leading to death was low in the pooled enzalutamide groups (4.8%) and in the placebo group (2.8%) and the adjusted event rates for serious TEAEs were also comparable in both groups.

The incidence of TEAEs leading to permanent discontinuation of study drug was similar in both groups; 17.2% in the pooled enzalutamide groups and 16.1% in the placebo group. The incidence of TEAEs leading to a dose reduction was 5.6% in the phase 3 enzalutamide group and 2.0% in the phase 3 placebo group. The incidence of TEAEs leading to a dosing interruption was 15.0% in the phase 3 enzalutamide group and 9.9% in the phase 3 placebo group.

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 MDV3100-03 (PREVAIL) in asymptomatic or mildly symptomatic subjects and CRPC2 (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 demonstrate 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 MDV3100-03 (PREVAIL) showed a significant benefit of enzalutamide in time to initiation of cytotoxic chemotherapy.

Study MDV3100-03 (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).

Study CRPC2 (AFFIRM; postchemotherapy mCRPC subjects) demonstrated that enzalutamide treatment decreased the risk of death by 37% (HR, 0.631; $P < 0.0001$) 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 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 $\geq 80\%$ decline in PSA from baseline at week 25. Of the 54 patients who were on treatment for 1 year (week 49), 100% had a $\geq 80\%$ decline in PSA from baseline. Eleven (42.3%) of 26 evaluable patients with metastatic disease at study entry had a derived objective response (confirmed complete response + confirmed partial response), 8 (30.8%) patients with confirmed complete response, and 3 (11.5%) patients with confirmed partial response.

The primary efficacy analysis in PROSPER demonstrated a statistically significant, robust and substantial improvement in metastasis-free survival together with clinically meaningful improvements in the key secondary endpoints of time to PSA progression and time to first use of new antineoplastic therapy and a trend in OS in favor of enzalutamide treatment. The

final OS analysis demonstrated a statistically significant and clinically meaningful improvement favoring enzalutamide and a 26.6% reduction in the risk of death.

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, there are 4 important identified risks associated with enzalutamide (seizure, fall, nonpathological fracture and ischemic heart disease). 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 mCRPC who are hormone sensitive. As described in [Section 10.1](#), a Data Safety Monitoring Board (DSMB) 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 advanced 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 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 rPFS based on central review

2.1.2 Secondary Objectives

- To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by OS
- 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 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]), in particular by:
 - time to deterioration in urinary symptoms using a modified urinary symptoms scale from QLQ-PR25 [\[Section 7.4.2 Analysis of Secondary Endpoints\]](#)
 - time to deterioration in QoL using the FACT-P global score
- 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 time to PSA progression
- 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)
- 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])

2.1.3 Safety Objective

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

2.1.4 Exploratory Objective (North America sites only)

- To determine gene mutations potentially related to resistance of enzalutamide plus ADT as assessed by DNA mutation testing in plasma

2.2 Study Design and Dose Rationale

2.2.1 Study Design

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

Approximately 1100 subjects will be randomized centrally 1:1, and the randomization will be stratified by volume of disease (low versus high) and prior docetaxel therapy for prostate cancer (no prior docetaxel, 1-5 cycles, 6 cycles). 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.

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 5.3.1.1 Computed Tomography (CT)/Magnetic Resonance Imaging (MRI) and Bone Scan] or starting an investigational agent or new therapy for treatment of prostate cancer. It is recommended that subjects remain on study treatment until radiographic progression is confirmed by independent central imaging review. Subjects who discontinue study treatment without radiographic progression will continue to follow the radiographic assessment schedule until radiographic progression event is confirmed by the central imaging independent reviewer or until the target number of progression events is reached as assessed by the central review. All subjects will be followed for OS until the final OS analysis. Once the final number of events has been reached to trigger the final OS analysis, survival follow-up will be considered complete and subjects will be discontinued from long term follow-up. At the time of primary endpoint analysis and recommendation of the DSMB on study continuation, subjects may be asked to continue their open-label treatment in another Astellas-sponsored study.

Study films (CT/MRI and bone scan) should be read on site and also be submitted in digital format to the sponsor-designated facility for independent central review. 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 5.3.1.1 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. Once the final number of events has been reached to trigger the final OS analysis, sites will no longer be required to collect EQ-5D-5L, QLQ-PR25, FACT-P for QoL and BPI-SF.

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

An independent DSMB will monitor the safety data on an ongoing basis.

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. All subjects are to be followed for survival until death, loss to follow-up, withdrawal of consent, or study termination by the sponsor. At the time of consent, staff will collect contact information for secondary contacts and other country-specific subject identifying information for purposes of assisting the site with determination of subject survival status. Once a sufficient number of death events has been reached for the OS analysis, survival follow-up will be considered complete and the long term follow-up process and QoL assessments collection will discontinue for all study participants.

Subjects who are continuing to receive clinical benefit from treatment with enzalutamide after the OS analysis data cutoff or at study termination and have not met any discontinuation criteria may continue their open-label treatment in another Astellas-sponsored study.

Subjects who choose not to continue open-label treatment in another Astellas-sponsored study after the OS analysis data cutoff will discontinue from treatment and complete a 30-day follow-up visit from the last dose of enzalutamide or prior to the initiation of another anticancer therapy, 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 data gathered from the ARCHES study may be used to support future research studies.

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

- rPFS (based on central review)

2.3.2 Secondary Endpoints

- OS
- Time to first SSE
- Time to castration resistance
- Time to deterioration of QoL
- Time to deterioration in urinary symptoms

- Time to initiation of new antineoplastic therapy
- Time to PSA progression (≥ 2 ng/mL) (Prostate Cancer Clinical Trials Working Group 2 criteria)
- PSA undetectable rate (< 0.2 ng/mL)
- ORR
- Time to pain progression

2.3.3 Safety Endpoints

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

2.3.4 Exploratory Endpoint (North America sites only)

- Mutation status in plasma of genes potentially related to resistance of enzalutamide plus ADT

3 STUDY POPULATION

3.1 Selection of Study Population

The study population will include approximately 1100 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 (e.g., Health Insurance Portability Accountability Act authorization for United States sites) 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. Specific to subjects enrolled in France, histological diagnosis is required.
4. Subject has metastatic prostate cancer documented by positive bone scan (for bone disease) or 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 and his female partner who is of childbearing potential must use 2 acceptable methods of birth control (1 of which must include a condom as a barrier method of contraception) from screening through 3 months after the last dose of study drug. Two acceptable methods of birth control include condom (barrier method is required) AND 1 of the following:
 - Consistent and correct usage of established, proper use of hormonal contraceptives that inhibit ovulation by the female partner;
 - Established intrauterine device or intrauterine system by the female partner;
 - Tubal ligation in the female partner performed at least 6 months prior to subject's screening visit;
 - Vasectomy or other procedure resulting in infertility (e.g., bilateral orchiectomy) performed at least 6 months prior to screening;
 - Calendar-based contraceptive methods (Knaus-Ogino or rhythm method applicable to subjects enrolled in Japan only).
10. Subject must use a condom throughout the study if engaging in sexual intercourse with a pregnant woman.
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 antiprostata 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/ μ L, platelet count < 100000/ μ L 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) \geq 1.5 x the upper limit of normal (ULN) (except subjects with documented Gilbert's disease), or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) \geq 2.5 x the ULN at screening.
 13. Subject has creatinine > 2 mg/dL (177 μ mol/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 \geq 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 \leq 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 Test 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).

Enzalutamide capsules should be swallowed whole and should not be chewed, dissolved or opened. Enzalutamide capsules can be taken with or without food. Enzalutamide capsules should not be handled by persons other than the patient or his caregivers. Based on its mechanism of action and embryo-fetal toxicity observed in mice, enzalutamide may harm a developing fetus. Women who are or may become pregnant should not handle damaged or opened enzalutamide capsules without protection, e.g., gloves. See nonclinical safety data in [Section 1.2.1](#). Enzalutamide capsules should be kept out of the reach of children.

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 (68°F to 77°F); excursions from 15°C to 30°C (59°F to 86°F) are permitted. Subjects will be instructed to store study drug in the original bottle at room temperature out of the reach of children.

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 (68°F to 77°F); excursions from 15°C to 30°C (59°F to 86°F) are permitted. Subjects will be instructed to store study drug in the original bottle at room temperature out of the reach of children.

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)- Astellas United States Technologies, Inc (AUST) or sponsor's designee in accordance with APGD-AUST 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.

A qualified person of Astellas Pharma Europe B.V. (APEBV) or sponsor's designee will perform the final release of the medication according to Directive 2003/94/EC annex 13.

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, and;
- 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, head of study site (specific to sites in Japan) or designee. Study drug accountability throughout the study must be documented and reconciled. The following guidelines are therefore pertinent:

- The investigator, head of study site (specific to sites in Japan) 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, head of study site (specific to sites in Japan) 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, head of study site (specific to sites in Japan) 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, head of study site (specific to sites in Japan) 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

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).

4.4.1 Blinding Method

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.

4.4.2 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.

The DSMB will be provided access to the dosing assignment for periodic review of the unblinded data as documented in the DSMB Charter.

4.4.3 Breaking the Treatment Code

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.

Unblinding of the study treatment assignment may be performed if the subject discontinues from the study treatment due to disease progression (must be confirmed by central review) and in the judgment 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.

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.

4.4.4 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 1:1 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 (None, 1-5 cycles, 6 cycles) 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.

Subjects who are continuing to receive clinical benefit from treatment with enzalutamide after the OS analysis data cutoff or at study termination and have not met any discontinuation criteria may continue their open-label treatment in another Astellas-sponsored study.

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 [\[Appendix 12.1 List of Excluded Concomitant Medications\]](#). 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;
- Biologic or other agents with potential 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 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.

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 is less than 80% 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.

5.2 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 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 should also be submitted if digital format images are available for submission to the sponsor designated facility for independent central review.

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 for independent central review. 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 by independent central imaging review. Subjects will continue to be scanned every 12 weeks until radiographic progression is confirmed by independent review or the number of progression events is reached.

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 Subject Reported Outcomes

Subject reported outcomes will be collected according to the schedule of assessments [Table 1, Table 4 (Open Label) and Table 5 (Study Continuation)].

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 Adverse Events

AE collection will begin at the time the informed consent form (ICF) is signed and continue until subject is determined to be ineligible for study entry, or initiation of new therapy for prostate cancer, or 30 days after the last dose of study drug, whichever occurs first.

See [Section 5.5 Adverse Events and Other Safety Aspects] for information regarding AE collection and data handling.

5.4.2.1 Adverse Events of Possible Hepatic Origin

See [Appendix 12.2 Liver Safety Monitoring and Assessment] for detailed information on liver abnormalities, monitoring and assessment, if the AE for a subject enrolled in a study and receiving study drug is accompanied by increases in LFTs (e.g., AST, ALT, bilirubin, etc.) or is suspected to be due to hepatic dysfunction. Subjects with AEs of hepatic origin accompanied by LFT abnormalities should be carefully monitored.

5.4.3 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]. Samples will be analyzed at sponsor designated central laboratory. Analytes included are identified in [Table 3].

Table 3 Laboratory Assessments

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

Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator/subinvestigator who is a qualified physician.

5.4.4 Physical Examination including Weight and Height

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].

5.4.5 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.

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events

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

Some countries 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.

Clinical signs or symptoms of disease progression will be recorded as AEs. However, disease progression itself should not be recorded as an AE unless the disease progression results in death; this event is recorded as an AE with 'disease progression' as the reported term.

5.5.2 Definition of Serious Adverse Events

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.

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

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

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

All of the special situations noted above should be recorded on the eCRF. Any situation involving these events that also meets the criteria for an SAE should be recorded on the AE page of the eCRF and marked ‘serious’ on the SAE worksheet/report.

The sponsor has a list of events that they classify as “always serious” events. If an AE is reported that is considered to be an event per this classification as “always serious,” additional information on the event may be requested.

5.5.3 Criteria for Causal Relationship to the Study Drug

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

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

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

In the case of a SAE, the investigator must contact the sponsor by fax or email immediately (within 24 hours of awareness).

The investigator should complete and submit an SAE Worksheet containing all information that is required by the Regulatory Authorities to the sponsor immediately (within 24 hours of awareness). If the submission of an SAE Worksheet is not possible or is not possible within 24 hours, the local drug safety contact should be informed by phone.

Specific to sites in Japan, in the case of a SAE, the investigator or subinvestigator must report to the head of the study site and must contact the sponsor by telephone or fax immediately (within 24 hours of awareness).

The investigator should complete and submit JUTOKUNA YUUGAIJISHOU HOUKOKUSHO containing all information that is required by the Regulatory Authorities to the sponsor by fax immediately (within 24 hours of awareness) and to the head of the hospital. If the faxing of JUTOKUNA YUUGAIJISHOU HOUKOKUSHO is not possible or is not possible within 24 hours, the sponsor should be informed by phone.

For contact details, see [\[Section II Contact Details of Key Sponsor's Personnel\]](#). Fax or email the SAE Worksheet to:

Astellas Pharma Global Development, Inc – United States
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

Specific to sites in Japan, fax the SAE worksheet (JUTOKUNA YUUGAIJISHOU HOUKOKUSHO) to:

Astellas Pharma Inc – Japan
Japan/Asia Clinical Development
Fax: 03-3243-5737

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 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

The sponsor or sponsor's designee will submit expedited safety reports (i.e., IND Safety Reports) to the regulatory agencies (i.e., FDA) as necessary, and will inform the investigators of such regulatory reports. Investigators must submit safety reports as required by their IRB/local IEC within timelines set by regional regulations (i.e., EU, eCTD, FDA).

Documentation of the submission to and receipt by the IRB/local IEC of expedited safety reports should be retained by the site.

The sponsor or designee will notify all investigators responsible for ongoing clinical studies with the study drug of all SAEs which may require submission to the IRB/local IEC/head of the study site per local requirements.

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

Specific to sites in Europe, for SUSAR from a blinded trial, unblinded Council for International Organizations of Medical Sciences (CIOMS)-I report will be submitted to the authorities and IRB/Central IEC where required.

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.

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

Refer to [\[Appendix 12.2 Liver Safety Monitoring and Assessment\]](#) for detailed instructions on Drug Induced Liver Injury.

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 [\[Appendix 12.3 Common Serious Adverse Events\]](#) 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 [\[Appendix 12.3 Common Serious Adverse Events\]](#). 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 Procedure in Case of 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.

5.5.9 Emergency Procedures and Management of Overdose

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.

All overdose events are to be reported within 24 hours of awareness as per [[Section 5.5.2 Definition of Serious Adverse Events](#)].

5.5.10 Supply of New Information Affecting the Conduct of the Study

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

The following 2 paragraphs are specific to sites in Japan:

1. When information is obtained regarding serious and unexpected adverse drug reactions (or other) that are specified in Article 273 of the Enforcement Regulations of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics, in compliance with Article 80-2 Paragraph 6 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics, the sponsor should inform all the investigators involved in the clinical study, the head of the study site, and the regulatory authorities of such information. The head of the study site who receives such

information will decide whether the clinical study should be continued after hearing the opinions of the IRB. The investigator will supply the new information to the subjects, in compliance with [\[Section 8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information\]](#).

2. In addition to the above item (1), when the head of the study site receives the revisions of the Investigator's Brochure, protocol, or written information, information on the matters covering the quality of the study drug, efficacy and safety, information necessary for conducting the clinical study properly, or documents to be examined by the IRB should be sent to the IRB.

5.5.11 Deviations from the Protocol and Other Actions Taken to Avoid Life-threatening Risks to Subjects (Specific to Sites in Japan)

The investigator must not deviate from or amend the protocol, excluding an emergency case for avoiding risks to the subjects. When the investigator does not follow the protocol in order to avoid urgent risks for subjects, the investigator should take the following actions.

1. Describe the contents of the deviation or amendment and the reasons for it in a written notice, and immediately send the document stating the deviation or amendment and the reasons to the sponsor and the head of the study site. Keep a copy of the notice.
2. Consult with the sponsor at the earliest possibility for cases in which it is necessary to amend the protocol. Obtain approval for a draft of the amended protocol from the IRB and the head of the study site as well as written approval from the sponsor.

5.6 Test Drug Concentration

Not applicable.

5.7 Other Measurements, Assessments or Methods

5.7.1 Optional Blood Sample for Mutation Analysis (North America Sites Only)

At randomization, at week 49, and at study treatment discontinuation, a 10 mL whole blood sample will be collected for subjects who are randomized in North America and provide consent.

Whole blood will be processed to plasma using standard centrifugation methods. Analysis methods [\[Romanel et al, 2015; Azad et al, 2015\]](#) will be adapted and used to perform a targeted mutation evaluation of specific target genes including, AR, epidermal growth factor receptor (EGFR), neuroblastoma RAS viral oncogene homolog (NRAS), Kirsten rat sarcoma viral oncogene homolog (KRAS), phosphatidylinositol-4, 5-bisphosphate 3-kinase and catalytic subunit alpha (PIK3CA). Other genes potentially related to resistance to enzalutamide may be analyzed.

Samples will be shipped to a sponsor designated laboratory for analysis. Details on sample collection, labeling, storage and shipment procedures will be provided in a separate laboratory manual.

5.7.2 Optional Blood Sample for Future Pharmacogenomic Analysis (Retrospective Pharmacogenomic Analysis)

Pharmacogenomic (PGx) research may be conducted in the future to analyze or determine genes of relevance to clinical response and toxicity/safety issues. After randomization [Table 1], a 5 mL sample of whole blood for possible retrospective PGx analysis will be collected using a vacutainer tube containing EDTA for subjects who provide consent. Samples will be shipped to a sponsor designated laboratory for sample banking.

Details on sample collection, labeling, storage and shipment procedures will be provided in a separate laboratory manual.

See [Appendix 12.4, Retrospective PGx Substudy] for further details on the banking procedures.

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 30 mL. Approximately 10 mL will be drawn at each subsequent study visit while on study drug. For those subjects randomized in North America who agree to provide samples for mutation analysis, an additional 10 mL sample will be collected at each time point of day 1, week 49 and at study treatment discontinuation.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

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 by the independent reader 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) as confirmed by the central laboratory.
- 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.
- Final analysis for OS completed.
- Study termination by the sponsor.

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor and, specific to sites in Japan, the head of the study site must also be informed immediately.

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

The statistical analysis will be coordinated by the responsible biostatistician from Astellas. 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 1100 subjects (550 subjects per treatment arm) will be randomized in the study.

The final analysis of rPFS will be conducted with a minimum of 262 progression events based on the following considerations:

- A target HR is 0.67. The expected median rPFS for the ADT arm is 20 months as measured from the date of randomization. A target HR of 0.67 corresponds to approximately 50% increase in median rPFS for the enzalutamide plus ADT arm relative to the placebo plus ADT arm (approximately 30 versus 20 months).
- The required minimum of 262 rPFS events (radiographic progression or death on study, defined as death from any cause within 24 weeks after treatment discontinuation, whichever occurs first) provides 90% power to detect a target HR of 0.67 based on a 2-sided log-rank test and significance level of 0.05.

Additionally the study is powered for OS. Specifically, 342 death events will be required to provide 80% power to detect a target hazard ratio of 0.73 with a target difference in Kaplan-Meier estimated median of approximately 15 months (40 months for placebo versus 55 months for enzalutamide) at the 4% significance level. This significance level was chosen to apply a parallel testing strategy between OS and some other secondary endpoints (with allocated type I error rate of 1%) as described in [Section 7.4.2](#).

7.2 Analysis Set

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

rPFS is defined as the time from randomization to the first objective evidence of radiographic disease progression as assessed by central review 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 effect of enzalutamide plus ADT compared to ADT will be tested using a stratified log-rank test at the level of significance of 0.05 (2-sided). 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 rPFS. Median duration of rPFS will be estimated using the corresponding 50% percentile of the Kaplan-Meier estimates. A 2-sided 95% CI will be provided for these estimates.

The analysis will be conducted when at least 262 rPFS events have occurred.

7.4.1.1 Subgroup Analysis

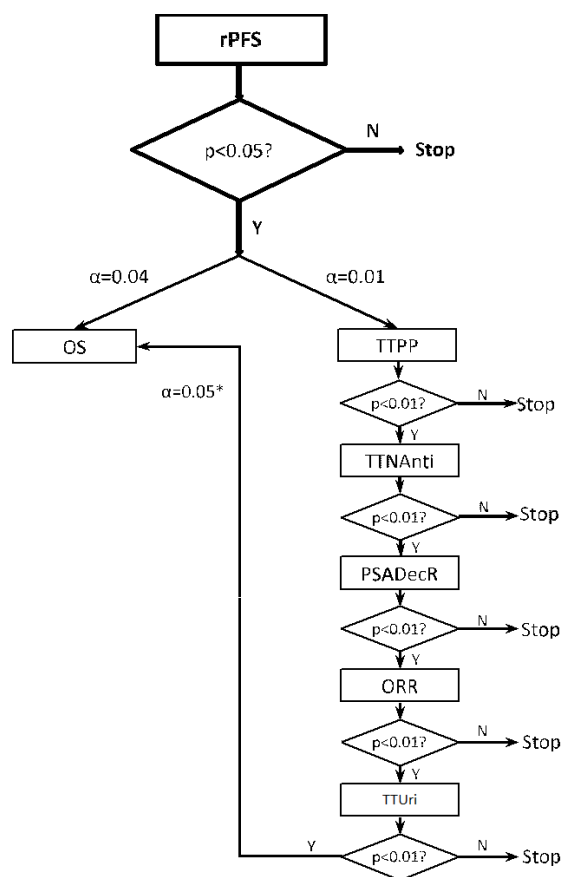
Subgroup analyses of rPFS will be conducted to assess the consistency of the treatment effect across the subgroups.

7.4.2 Analysis of Secondary Endpoints

All secondary endpoint analyses will be performed at the time of the rPFS final analysis.

The following 6 secondary endpoints will be tested: OS, time to PSA progression (TTPSA), time to initiation of a new antineoplastic therapy (TTN_{Anti}), the rate of PSA decline to < 0.2ng/mL (PSADecR), the objective response rate (ORR) and time to deterioration in urinary symptoms (TTU_{ri}). A parallel testing strategy between OS (with allocated type I error rate 0.04) and the other 5 endpoints (with allocated type I error rate 0.01) will be performed, as summarized in [Figure 2](#).

Figure 2 Testing Strategy for the Primary and 6 Selected Secondary Endpoints



OS: overall survival; ORR: objective response rate; PSADecR: rate of PSA decline to < 0.2 ng/mL; rPFS: radiographic progression-free survival; TTNAnti: time to initiation of a new antineoplastic therapy; TTPSA: time to PSA progression; TTUri: time to deterioration in urinary symptoms from the QLQ-PR25.

*OS will be tested at 0.05 only if the other 5 secondary endpoints analyses are statistically significant at 0.01.

Details of the primary and the selected secondary endpoints testing as a step-by-step approach will be described in the Statistical Analysis Plan (SAP).

One interim analysis and a final analysis are planned for OS. The interim analysis of OS will be performed at the time of the rPFS final analysis. If this interim analysis of OS is statistically significant, it will be reported as the final analysis and no subsequent analysis will be performed. At the time of the planned final analysis of OS, no additional analyses of other efficacy endpoints will be conducted.

OS:

The duration of OS is defined as the time from randomization to death from any cause. OS will be analyzed as for rPFS.

The O'Brien-Fleming alpha spending function will be used to determine the stopping boundaries based on the number of events observed at the interim look to control the overall 2-sided alpha at 0.05 or at 0.04 (as described in Figure 2).

The interim analysis of OS expected at the time of the final analysis of rPFS will be performed at an expected significance level of 0.006 based on approximately 170 death events. If this interim analysis of OS is not statistically significant, the final analysis of OS is planned when approximately 342 deaths are observed to ensure an adequate number of events for the evaluation of OS.

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 rPFS.

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 rPFS.

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 rPFS.

Time to deterioration in urinary symptoms:

A deterioration in urinary symptoms is defined as an increase in urinary symptoms scores, using a modified urinary symptoms scale derived from a selected subset of symptoms from the QLQ-PR25 questionnaire module (including 3 items: Q31 - Q33), by $\geq 50\%$ of the standard deviation observed in the modified urinary symptoms scale score at baseline [Tombal et al, 2018]. Time to deterioration in urinary symptoms is defined as time from randomization to the first deterioration in urinary symptoms. The analysis method will be the same as for rPFS.

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 rPFS.

Time to PSA progression:

Time to PSA progression is defined as a $\geq 25\%$ 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 method of analysis for time to PSA progression will be the same as for rPFS.

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. 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. Only subjects with measurable soft tissue disease at baseline will be included in this analysis.

Time to pain progression:

Pain progression is defined an increase of $\geq 30\%$ 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 rPFS.

Time to event endpoints such as rPFS, time to PSA progression, OS, time to first SSE, time to castration resistance, time to deterioration of QoL, time to deterioration in urinary symptoms, 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 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 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 TEAEs.

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 Electrocardiogram

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.

7.6 Analysis of Exploratory Endpoint

An exploratory mutation analysis of specific gene targets including AR, EGFR, NRAS, KRAS, and PIK3CA will be conducted for samples collected in North America. Other genes potentially related to resistance to enzalutamide may be analyzed. Mutations status will be summarized by descriptive statistics, including number of subjects, variant frequency, mean, standard deviation, minimum, median and maximum, and individual mutation status over time will be evaluated.

7.7 Analysis of Pharmacokinetics

Not applicable.

7.8 Protocol Deviations and Other Analyses (Unique to JP: Other Analyses)

Protocol deviations as defined in [\[Section 8.1.6 Protocol Deviations\]](#) 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 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,

7.9 Interim Analysis

No formal interim analysis is planned for rPFS. One interim analysis of OS will be performed at the time of the rPFS final analysis. If this interim analysis of OS is statistically significant, it will be reported as the final analysis and no subsequent analysis will be performed.

7.10 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 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

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

Laboratory tests are performed at the sponsor designated central laboratory. Laboratory data will be transferred electronically to the sponsor or designee at predefined intervals during the study. The laboratory will provide the sponsor or designee with a complete and clean copy of the data.

Independent central imaging review results are performed at a sponsor designated central imaging review facility. Central imaging review data will be transferred electronically to the sponsor or designee at predefined intervals during the study. The central imaging review facility will provide the sponsor or designee with a complete and clean copy of the data.

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.

8.1.2 Specification of 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. Unless otherwise specified, source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

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

- Demographic data (age, gender, race, ethnicity, height and body weight);
- Inclusion and exclusion criteria details;
- Participation in study and original signed and dated ICFs;
- Visit dates;
- Medical history and physical examination details;
- Key efficacy and safety data as specified in the protocol;
- AEs and concomitant medication;
- Results of relevant examinations (e.g., ECG charts, X-ray films etc.);
- Laboratory printouts;
- Dispensing and return of study drug details;
- Reason for premature discontinuation (if applicable);
- Randomization number (if applicable);
- Staff notes and telephone conversation documentation;
- Medical records from other departments or hospitals (photocopy or faxed document of original record is acceptable if obtained from an outside institution).

8.1.3 Clinical Study Monitoring

The sponsor or designee 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/subinvestigator are accurate and complete and that they are verifiable with study-

related records such as source documents. The sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.4 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the sponsor or designee as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents (refer to [\[Section 8.1.2 Specification of Source Documents\]](#)) 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.

8.1.5 Data Management

Data management will be coordinated by the Data Science department 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 Drug Dictionary, respectively.

8.1.6 Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety and welfare of 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.

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

- Entered into the study even though they did not satisfy entry criteria;
- Developed withdrawal criteria during the study and not withdrawn;
- Received wrong treatment or incorrect dose;
- Received excluded concomitant treatment.

When a 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 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.

8.1.7 End of Trial in All Participating Countries

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

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 IRB/IEC/Competent Authorities

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

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

If required by local regulations, the investigator shall make accurate and adequate written progress reports to the IEC/IRB at appropriate intervals, not exceeding 1 year. The investigator shall make an accurate and adequate final report to the IRB/IEC within 90 days after the close-out visit for APGD-sponsored studies.

8.2.2 Ethical Conduct of the Study

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

8.2.3 Informed Consent of Subjects

8.2.3.1 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 (specific to sites in Japan, place a personal seal) 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 (specific to sites in Japan, or sealed) 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.

8.2.3.2 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 reobtain consent 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 (specific to sites in Japan, place a personal seal). A copy of the signed (specific to sites in Japan, or sealed) 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 reobtain process.

8.2.4 Subject Confidentiality

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

8.3 Administrative Matters

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

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

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

8.3.2 Documents and Records Related to the Clinical Study

The sponsor will provide the investigator and/or institution with the following:

- Study protocol (and amendments, where applicable);
- Investigator's Brochure (and amendments, where applicable);
- eCRFs;
- JUTOKUNA YUUGAIJISHOU HOUKOKUSHO (specific to sites in Japan);
- Study drug with all necessary documentation;
- Study contract.

In order to start the study, the investigator and/or study site is required to provide the following documentation to the sponsor:

- Financial disclosure in compliance with federal regulation 21CFR Part 54;
- Signed and dated FDA form 1572, if conducted under a U.S. IND;
- Signed Investigator's Statement in this protocol and eCRF;
- Current Curricula Vitae of all investigators;
- List of subinvestigators and collaborators;
- IRB approval of the protocol, protocol amendments (if applicable) including a membership list with names and qualification;
- Instruction and decision of the head of the study site (specific to sites in Japan);
- Study contract;
- Laboratory normal reference ranges (if applicable, signed and dated by the responsible laboratory employee).

The investigator will archive all study data (e.g., Subject Identification Code List, source data, CRFs and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (for US sites, 2 years after approval of the NDA or discontinuation of the IND). The sponsor will notify the site/investigator if the NDA/MAA/J-NDA is approved or if the IND/IMPd/CHIKEN TODOKE 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.

Specific to sites in Japan, the records to be retained at the study sites are the ones listed as essential documents in GCP. These records shall be retained by the head of the study site or the record keeper designated by the head until notice issued by the sponsor on completion of the retention period is received. These documents are also subject to direct access and should be provided upon request from the sponsor or regulatory authorities.

Specific to sites in Japan, the head of the study site will retain the essential documents that should be stored at the study site in an appropriate manner according to the rules of the study site concerned until the date defined in 1 or 2 below, whichever comes later.

1. Approval date of marketing of the test drug (if development of the drug is stopped, until 3 years after the decision to discontinue development is notified);
2. Until 3 years after discontinuation or termination of the study.

The following are the major documents to be retained at the study site.

1. Source documents (e.g., clinical data, documents, and records for preparing the CRF, hospital records, medical records, test records, memoranda, subject diary or check lists for evaluation, administration records, data recorded by automatic measuring instruments, reproductions or transcripts verified as precise copies, microfiche, negative films, microfilms/magnetic media, X-ray films, subject files and study-related records kept at

- either a pharmacy, a laboratory, or medical technical office, as well as subject registration forms, laboratory test slips including central measurement, worksheets specified by the sponsor, records of clinical coordinators, and records related to the clinical study selected from those verified in other departments or hospitals).
2. Contracts, written ICFs, written information, and other documents or their copies prepared by the study personnel. A letter of request for clinical study (including a request for continuation/amendment), letter of request for review, notice of clinical study contract, clinical study contract, notification of discontinuation or completion of clinical study, written information for informed consent (including revisions), signed and dated written informed consent (including revisions), CVs of investigators, list of subinvestigators, list of signatures and print of seals (copy), and CRFs (copy), etc.
 3. The protocol, documents obtained from the IRB related to the adequacy of conducting the clinical study by the head of the study sites (Article 32-1, MHW Ordinance No. 28), documents obtained from the IRB related to the adequacy of conducting a clinical study whose period exceeds 1 year or the adequacy of continuously conducting the clinical study from which information on adverse drug reactions is obtained, and other documents obtained. An agreed-upon protocol (including revisions), Investigator's Brochure (including revisions), operational procedures for the investigator, materials and information supplied by the sponsor (e.g., AE report), matters reported by the investigator (revisions of the protocol, AE reports, etc.), operational procedures for the IRB, the list of names of the IRB members, materials for IRB review (including continuous deliberation), IRB review records (including continuous deliberation), and the review result report of the IRB (including continuous deliberation), etc.
 4. Records of control for study drugs and other duties related to the clinical study. Procedure for controlling the study drugs, drug inventory and accountability record, vouchers for the receipt and return of the study drugs, and the prescriptions for concomitant medications

The documents of the Efficacy and Safety Evaluation Committee (minutes and SOPs and others) and the judgment committee outside the study sites (minutes and SOPs and others) shall be retained by the sponsor.

8.3.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or 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.

8.3.4 Insurance of Subjects and Others

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

Specific to sites in Japan, if a subject suffers any study-related injury, the sponsor will compensate appropriately according to the severity and duration of the damage. However, if it was caused intentionally or was due to gross negligence by the study site, the sponsor will consult with the study site about handling the injury, based on the agreed study contract.

Specific to sites in Japan, compensation for the study-related injury is provided by the following procedures:

1. If a subject incurs an injury as a result of participation in the clinical study, the study site should provide medical treatment and other necessary measures. The sponsor should be notified of the injury.
2. When the subject claims compensation from the study site for the above study-related injury, or such compensation may be claimed, the study site should immediately communicate the fact to the sponsor. Both parties should work together towards compensation settlement.
3. The sponsor shall pay compensation or indemnification and bear expenses necessary for the settlement as provided in the clinical contract.
4. The sponsor shall make an arranging for insurance and take measures necessary to ensure the compensation or indemnification mentioned above.

8.3.5 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final study report which forms part of a marketing authorization application be signed by the representative for the Coordinating Investigator(s) or the Principal Investigator(s). The representative for the Coordinating Investigator (s) or the Principal Investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for Coordinating Investigator(s) or the Principal Investigator(s) will be selected from the participating investigators by the sponsor prior to database lock.

9 QUALITY ASSURANCE

The 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.

10 STUDY ORGANIZATION

10.1 Data Safety Monitoring Board

A DSMB will evaluate the unblinded safety data of subjects enrolled on a periodic basis during this study. DSMB members will be clinicians with expertise in prostate cancer trials and are not investigators participating in this trial or Astellas employees. A separate charter will outline the activities of this committee.

10.2 Other Study Organization

Specific to sites in Japan: the Japan site contact list is kept as a separate attachment to the protocol.

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12 APPENDICES

12.1 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;
- Biologic or other agents with potential 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 antiprostata 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.

12.2 Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases to $> 3 \times \text{ULN}$ (to $> 5 \times \text{ULN}$ in subjects with liver metastases), or bilirubin $> 2 \times \text{ULN}$, 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. For studies for which a central laboratory is used, alerts will be generated by the central lab regarding moderate or severe liver abnormality to 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	$> 3 \times \text{ULN}$ (in subjects without liver metastases), $> 5 \times \text{ULN}$ (in subjects with liver metastases)	or	$> 2 \times \text{ULN}$
Severe*	$> 3 \times \text{ULN}$	and	$> 2 \times \text{ULN}$

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

- ALT or AST $> 8 \times \text{ULN}$;
- ALT or AST $> 5 \times \text{ULN}$ for more than 2 weeks (in the absence of liver metastases);
- ALT or AST $> 3 \times \text{ULN}$ and INR > 1.5 (If INR testing is applicable/evaluated);
- ALT or AST $> 3 \times \text{ULN}$ 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 $> 8 \times$ ULN;
- ALT or AST $> 5 \times$ ULN for more than 2 weeks (in subjects without liver metastases);
- ALT or AST $> 3 \times$ ULN and TBL $> 2 \times$ ULN or INR > 1.5 (If INR testing is applicable/evaluated);
- ALT or AST $> 5 \times$ ULN and (TBL $> 2 \times$ ULN in subjects with liver metastases);
- ALT or AST $> 3 \times$ 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 x ULN elevations are too common in treated and untreated subjects to be discriminating”). 2. Cases of increased bilirubin (at least 2 x ULN) with concurrent transaminase elevations at least 3 x ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's syndrome [Temple, 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.

12.3 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 FDA. If aggregate analysis of these events indicates they occur more frequently with study drug, an expedited IND safety report may be submitted to the FDA.

- 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

12.4 Retrospective Pharmacogenomic Substudy

INTRODUCTION

PGx research aims to provide information regarding how naturally occurring changes in a subject's gene and/or expression based on genetic variation may impact what treatment options are best suited for the subject. Through investigation of PGx by technologies such as genotyping, gene sequencing, statistical genetics and Genome-Wide Association Studies, the relationship between gene profiles and a drug's kinetics, efficacy or toxicity may be better understood. As many diseases may be influenced by 1 or more genetic variations, PGx research may identify which genes are involved in determining the way a subject may or may not respond to a drug.

OBJECTIVES

The PGx research that may be conducted in the future with acquired blood samples is exploratory. The objective of this research will be to analyze or determine genes of relevance to clinical response, pharmacokinetics and toxicity/safety issues.

By analyzing genetic variations, it may be possible to predict an individual subject's response to treatment in terms of efficacy and/or toxicity.

SUBJECT PARTICIPATION

Subjects who have consented to participate in this study may participate in this PGx substudy. As part of this substudy, subjects must provide separate written consent prior to providing any blood samples that may be used at a later time for genetic analysis.

SAMPLE COLLECTION AND STORAGE

Subjects who consent to participate in this substudy will provide one 5 mL tube of whole blood per Astellas' instructions. Each sample will be identified by the unique subject number. Samples will be shipped frozen to a designated banking contract research organization either directly from site or via a central laboratory as directed by Astellas.

PGx ANALYSIS

Details on the potential PGx analysis cannot be established yet. Astellas may initiate the PGx analysis in case evidence suggests that genetic variants may be influencing the drug's kinetics, efficacy and/or safety.

DISPOSAL OF PGx SAMPLES/DATA

All PGx samples collected will be stored for a period of up to 15 years following study database hardlock. If there is no requirement for analysis, the whole blood sample will be destroyed after the planned storage period. The subject has the right to withdraw consent at any time. When a subject's withdraw notification is received, the PGx sample will be destroyed. The results of any PGx analysis conducted on a sample prior to its withdrawal will be retained at Astellas indefinitely.

INFORMATION DISCLOSURE TO THE SUBJECTS

Exploratory PGx analysis may be conducted following the conclusion of the clinical study, if applicable. The results of the genetic analysis will not be provided to any investigators or subjects, nor can the results be requested at a later date. Any information that is obtained from the PGx analysis will be the property of Astellas.

12.5 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.

12.6 Open-Label Extension

NOTE: The extension study described below and outlined in [Figure 3](#) Open-Label Extension schematic will be conducted if the ARCHES study results in a positive outcome. With the exception of those procedures and processes indicated below, this extension 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 extension section.

12.6.1 Rationale

Following unblinding at the end of the double-blind period and demonstration of a statistically significant advantage of enzalutamide over placebo when added to ADT, as assessed by the primary endpoint, all eligible subjects may be treated on study with open-label enzalutamide at the discretion of the subject and investigator.

Day 1 of the open-label extension will occur after consent is signed and eligibility is confirmed. Treatment with open-label enzalutamide will be stopped upon disease progression 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 12.6.6 Duration of Treatment and Criteria for Discontinuation](#)].

Subjects who do not participate in the open-label extension 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.

12.6.2 Schedule and Assessments

For procedures see [Table 4](#) (Open-Label Extension Schedule of Assessments).

Subjects treated with enzalutamide during the double-blind period will sign informed consent on Open-Label Day 1 and are required to return for study visits every 12 weeks (see [Figure 3](#) Open-Label Extension schematic). Subjects treated with placebo during the double-blind period will sign informed consent at the Open-Label Day 1 visit after which they will be switched to enzalutamide (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. All Open-Label Day 1 visits should occur within approximately 16 weeks after the approval and activation of this protocol amendment at the study site.

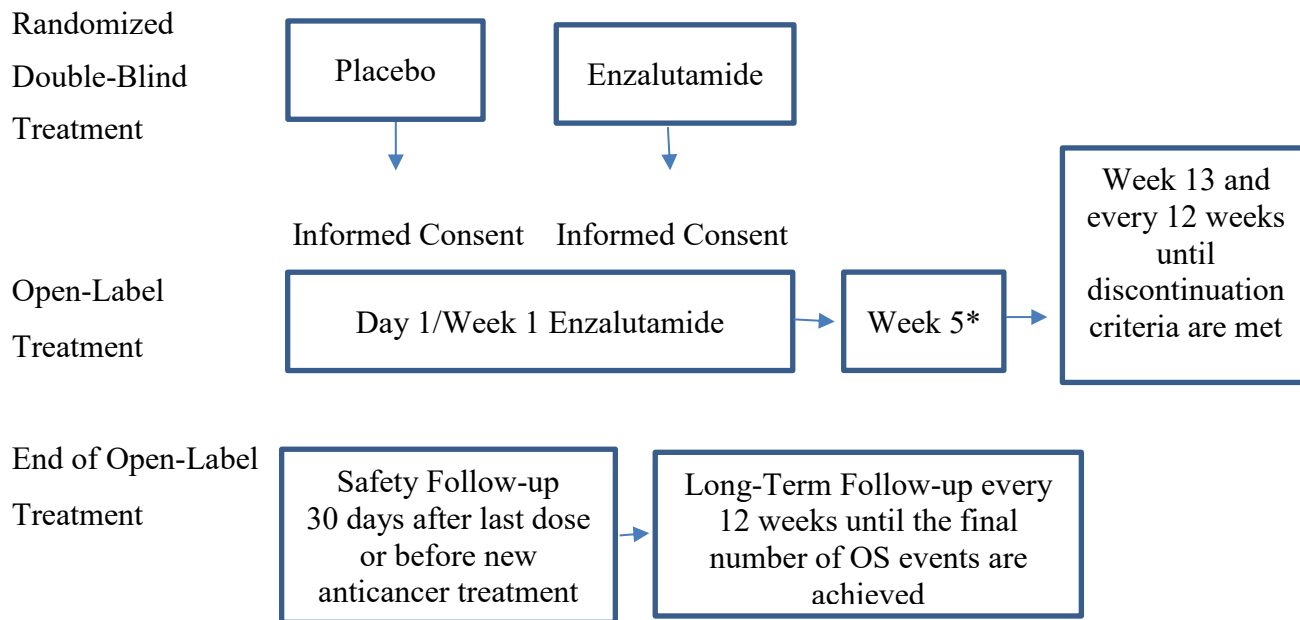
Subjects will take enzalutamide as four 40-mg soft gelatin capsules (160 mg/day) by mouth once daily with or without food. Subjects treated with enzalutamide during the double-blind period and dosed at a lower daily dose may continue at the lower dose as appropriate.

Study assessments will include safety evaluations including AEs, concomitant medications, clinical laboratory tests, brief physical examinations, ECGs and vital signs. Radiographic assessments (CT/MRI and bone scan) will be performed as per the Open-Label Extension Schedule of Assessments [[Table 4](#)] until the subject progresses radiographically based on local assessment and/or meets other treatment discontinuation criteria [[Section 12.6.6 Duration of Treatment and Criteria for Discontinuation](#)].

Subjects are to 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 until the completion of OS analysis. The information collected will include survival status, new antineoplastic therapies for prostate cancer, skeletal-related events and associated interventions.

Figure 3 Schematic – Open-Label Extension



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

Table 4 Open-Label Extension Schedule of Assessments

Study Period or Visit	OL Treatment ¹			Unscheduled Visit	OL Safety Follow-up	OL Long Term Follow-up ²
Study Week	OL 1 ³ (Day 1)	OL 5 ⁴ (Day 29)	OL 13 and Every Subsequent 12 Weeks (Day 85 and Every Subsequent 84 Days)	Varies ⁵	30 Days after Last Dose ⁶	Every 12 Weeks
Window (Days)	NA	± 3	± 5	NA	± 7	± 7
Informed Consent ⁷	X					
Inclusion/Exclusion for OLE	X					
Open-Label Enrollment (via IRT)	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	X	X	X	X	X	
Sample for Mutation Analysis ⁸	X		X ⁸			
Radiographic Assessments ⁹	X ⁹		X			
QoL Assessment (QLQ-PR25, EQ-5D-5L, FACT-P, Brief Pain Inventory-Short Form)	X		X		X	X ¹⁰
Adverse Events ¹¹	X	X	X	X	X	
Concomitant Medication Review	X	X	X	X	X	
Study Drug Dispensing (via IRT)	X	X	X			
Study Drug Accountability	X	X	X		X	
Long-Term Follow-up Assessments ²						X

ECOG: Eastern Cooperative Oncology Group; EQ-5D-5L: EuroQol Group-5 Dimension-5 Level Instrument; FACT-P: Functional Assessment of Cancer Therapy-Prostate; IRT: Interactive Response Technology; NA: not applicable; OL: Open-Label; OLE: Open-Label Extension; QLQ-PR25: Quality of Life Prostate-specific Questionnaire; QoL: Quality of Life.

Footnotes continued on next page

- 1 Subjects continuing into the Open-Label (OL) extension period may be asked to complete their extension period participation in another Astellas-sponsored study upon activation of the roll-over extension study. An OL 30-day follow-up visit is not required for subjects who choose to participate in the other Astellas-sponsored study.
- 2 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. This assessment will be collected until death, withdrawal of consent, final OS analysis or study termination.
- 3 For subjects previously receiving placebo, OL Day 1/Week 1 should occur within approximately 16 weeks after the approval and activation of this protocol at the study site and no later than 6 weeks after screening. For subjects continuing treatment with enzalutamide, OL Day 1/Week 1 will be their next regular scheduled visit following approval and activation of this protocol at the study site.
- 4 Only for subjects starting new treatment with enzalutamide (previously received placebo).
- 5 As necessary to assess or follow up adverse events.
- 6 Prior to initiation of new antineoplastic therapy for prostate cancer, or 30 days after last dose of enzalutamide, whichever occurs first.
- 7 Informed consent must be obtained before performing any study-specific procedures on Day 1/Week 1 for all subjects participating in OL Period
- 8 Blood samples for mutation analysis will be collected at sites in North America only in subjects who have previously signed a genotyping informed consent. For subjects starting new treatment with enzalutamide, samples will be collected on OL Day 1/Week 1 at OL Week 49 and at time of discontinuation of enzalutamide. Subjects previously treated with enzalutamide will have a final sample collected at the time of discontinuation of enzalutamide.
- 9 For subjects who have not progressed radiographically, scans (CT/MRI and bone scan) will be performed every 12 weeks for the first year on enzalutamide and then every 24 weeks until the subject has progressed radiographically, as assessed by local read.
- 10 QoL assessments will no longer be collected once the overall survival assessment is complete.
- 11 Adverse events will be collected from the time the subject signs the consent form until screen failure or through safety follow-up visit (prior to initiation of new antineoplastic therapy for prostate cancer, or 30 days after last dose of enzalutamide, whichever occurs first).

12.6.3 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. Subject received randomized double-blind treatment in ARCHES.
2. Subject has not met any of the discontinuation criteria in the main ARCHES protocol [[Section 6 Discontinuation](#)].
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.

12.6.4 Exclusion Criteria

The exclusion criteria apply only to subjects starting new treatment with enzalutamide after receiving placebo during double-blind period. Subjects will be excluded from participation if any of the following apply:

1. Subject has taken commercially available enzalutamide (Xtandi).
2. 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: Subjects who progressed radiographically while in the double-blind portion of the study and continued treatment per protocol are allowed to participate in the open label extension.)
3. After study-wide unblinding, subject has started any new investigational agent or anti-neoplastic therapy intended to treat prostate cancer.
4. 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.
5. Subject has current or previously treated brain metastasis or active leptomeningeal disease.
6. Subject has a history of seizure or any condition that may increase the risk of seizure.

12.6.5 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, unless they were receiving a reduced dose during double-blind treatment. Subjects previously receiving a reduced dose may continue at the reduced dose. 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.

12.6.6 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.
- Completion of final OS analysis.
- Death.

12.6.7 Statistical Methods

Subject disposition data (patients who continued to the open-label extension and primary reasons for treatment discontinuation and study discontinuation) will be summarized descriptively by study periods, in the ITT population for the blind study period and on patients who started open-label enzalutamide for the open-label extension.

Data collected in the open-label extension will only be summarized by descriptive statistics unless otherwise specified. Descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum for continuous endpoints, and frequency and percentage for categorical endpoints.

An open-label extension data summary will be presented for subjects who switched treatment from placebo+ADT to enzalutamide+ADT (i.e., subjects who received placebo+ADT during the blinded period). A combined double-blind and open-label data summary on

enzalutamide+ADT will be presented for all subjects who received enzalutamide+ADT either during the blind period or the open-label extension (i.e., overall).

Enzalutamide exposure will be summarized and listed in the open-label extension and in the combined double-blind and open-label, as 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.

A final OS analysis will be conducted after approximately 342 deaths are observed.

12.6.8 Phase 4 Post-marketing Study after Marketing Authorization in Japan (Sites in Japan Only)

In case that Enzalutamide is approved for marketing with the indication of mHSPC, the study will continue as “Phase 4 post-marketing study” in accordance with Good Post-marketing Study Practice (GPSP) after marketing authorization based on Notification No. 1061, dated 01 Dec 1998 by the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health. In this case, “Study” in the protocol is read as “Post-marketing study”. The formulation of 40-mg soft gelatin enzalutamide capsule will be switched to the 40 mg round film-coated oral tablet. The enzalutamide film-coated tablets contain hypromellose acetate succinate along with standard tableting excipients; microcrystalline cellulose, light anhydrous silicic acid, croscarmellose sodium, magnesium stearate. The tablets are film-coated using Opadry® yellow, which contains hypromellose, talc, polyethylene glycol 8000, titanium dioxide and yellow ferric oxide.

The clinical material is a solid drug product and is packaged in HDPE bottles with child-resistant closures. The tablets should be stored in original bottle at 20°C to 25°C (68°F to 77°F); excursions from 15°C to 30°C (59°F to 86°F) are permitted.

12.7 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 principal investigator discusses the need with the Astellas Medical Monitor 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 principal investigator or designee will obtain oral agreement from the subject followed by written documentation as soon as is feasible. A separate addendum to the study informed consent will be provided to document the participant's consent of the changes.

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 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 Assessment [Table 1](#) is expected, where plausible, in the case of a crisis. The alternate measures as noted in [Table 5](#) below are only permissible in the event of a crisis, and after discussing the need with the Astellas Medical Monitor to implement the alternate measures. This is to allow for continuity of receiving investigational medicinal product and maintaining critical safety and efficacy assessments for patients participating in the study at a time of crisis.

If one or more of the alternate measures noted below 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).

Table 5 Alternative Schedule of Assessments in Response to a Crisis

Study Period or Visit	Alternative Measures	OL Treatment ¹			Unscheduled Visit	OL Safety Follow-up	OL Long Term Follow-up ²
Study Week		OL 1 ³ (Day 1)	OL 5 ⁴ (Day 29)	OL 13 and Every Subsequent 12 Weeks (Day 85 and Every Subsequent 84 Days)	Varies ⁵	30 Days after Last Dose ⁶	Every 12 Weeks
Window (Days)	NA	NA	± 3	± 5	NA	± 7	± 7
Informed Consent ⁷		X					
Inclusion/Exclusion for OLE		X					
Open-Label Enrollment (via IRT)		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	Visit collection of samples at local facility acceptable if results can be made available to investigative site	X	X	X	X	X	
Sample for Mutation Analysis ⁸		X		X ⁸			
Radiographic Assessments ⁹		X ⁹		X			
QoL Assessment (QLQ-PR25, EQ-5D-5L, FACT-P, Brief Pain Inventory-Short Form)		X		X		X	X ¹⁰
Adverse Events ¹¹	Remote/Virtual/Telemedicine Visits allowed for non-dosing visits. Please refer to protocol schedule of assessments.	X	X	X	X	X	

Table continued on next page

Study Period or Visit	Alternative Measures	OL Treatment ¹			Unscheduled Visit	OL Safety Follow-up	OL Long Term Follow-up ²
Study Week		OL 1 ³ (Day 1)	OL 5 ⁴ (Day 29)	OL 13 and Every Subsequent 12 Weeks (Day 85 and Every Subsequent 84 Days)	Varies ⁵	30 Days after Last Dose ⁶	Every 12 Weeks
Concomitant Medication Review	Remote/Virtual/Telemedicine Visits allowed for non-dosing visits. Please refer to protocol schedule of assessments.	X	X	X	X	X	
Study Drug Dispensing (via IRT)	Courier service directly to patient allowed	X	X	X			
Study Drug Accountability		X	X	X		X	
Long-Term Follow-up Assessments ²	Remote/Virtual/Telemedicine Visits allowed. Please refer to protocol schedule of assessments.						X

AE: adverse event; CBC: complete blood count; ECG: electrocardiogram; ECOG: eastern cooperative oncology group; EOT: end of treatment; EQ-5D-5L: EuroQol Group-5 Dimension-5 Level Instrument; FACT-P: Functional Assessment of Cancer Therapy-Prostate; iCPD: “immune” confirmed progressive disease; IP: investigational product; IRT: Interactive Response Technology; NA: not applicable; OL: Open-Label; OLE: Open-Label Extension; QLQ-PR25: Quality of Life Prostate-specific Questionnaire; QoL: Quality of Life.

- Subjects continuing into the Open-Label (OL) extension period may be asked to complete their extension period participation in another Astellas-sponsored study upon activation of the other Astellas-sponsored study. An OL 30 day follow-up visit is not required for subjects who chose to participate in the other study.
- 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. This assessment will be collected until death, withdrawal of consent, final overall survival analysis, or study termination.
- For subjects previously receiving placebo, OL Day 1/Week 1 should occur within approximately 16 weeks after the approval and activation of this protocol at the study site and no later than 6 weeks after screening. For subjects continuing treatment with enzalutamide, OL Day 1/Week 1 will be their next regular scheduled visit following approval and activation of this protocol at the study site.
- Only for subjects starting new treatment with enzalutamide (previously received placebo).
- As necessary to assess or follow up adverse events.

Footnotes continued on next page

6. Prior to initiation of new antineoplastic therapy for prostate cancer, or 30 days after last dose of enzalutamide, whichever occurs first.
7. Informed consent must be obtained before performing any study-specific procedures on Day 1/Week 1 for all subjects participating in OL Period.
8. Blood samples for mutation analysis will be collected at sites in North America only in subjects who have previously signed a genotyping informed consent. For subjects starting new treatment with enzalutamide, samples will be collected on OL Day 1/Week 1 at OL Week 49 and at time of discontinuation of enzalutamide. Subjects previously treated with enzalutamide will have a final sample collected at the time of discontinuation of enzalutamide.
9. For subjects who have not progressed radiographically, scans (CT/MRI and bone scan) will be performed every 12 weeks for the first year on enzalutamide and then every 24 weeks until the subject has progressed radiographically, as assessed by local read.
10. QoL assessments will no longer be collected once the overall survival assessment is complete.
11. Adverse events will be collected from the time the subject signs the consent form until screen failure or through safety follow-up visit (prior to initiation of new antineoplastic therapy for prostate cancer, or 30 days after last dose of enzalutamide, whichever occurs first).

INVESTIGATIONAL MEDICINAL PRODUCT 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 investigational medicinal product supply to the participants:

- Increase stock of investigational medicinal product on site to reduce number of shipments required, if site space will allow.
- Direct-to-Participant shipments of investigational medicinal product 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 PROTOCOL AMENDMENT SUMMARY OF CHANGES

Version 5.1 Nonsubstantial Amendment 6 [18 APR 2022]

This amendment is considered to be nonsubstantial 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 and EU Clinical Trial Regulation because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

To extend the planned study period to the first quarter of 2024.

Summary of Changes

Table 6 Nonsubstantial Changes

Section Number	Description of Change	Brief Rationale
Cover Page	The date listed for Version 4.0 Substantial Amendment 3 is revised to 10 Dec 2018.	The date has been corrected.
IV	The planned study period is extended to the first quarter of 2024.	The study timeline has been extended to allow continued treatment until study subjects can enroll in Astellas Study 9785-CL-0123 at the respective study sites should the study site choose to participate in Study 9785-CL-0123.
12.6.2	Table 4 is moved to Section 12.6.2 Schedule of Assessments.	The location of Table 4 has been corrected.

14 SPONSOR'S SIGNATURES