A Multicenter, Single-Arm, Open-Label, Post-Marketing Safety Study to Evaluate the Risk of Seizure Among Subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Treated with Enzalutamide Who Are at Potential Increased Risk of Seizure (UPWARD)

ISN/Protocol 9785-CL-0403

ClinicalTrials.gov Identifier: NCT01977651

Date of Protocol v3.1: 20 Oct 2016

Sponsor: Astellas Pharma Global Development, Inc. (APGD)

1 Astellas Way

Northbrook, IL 60062

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Protocol for Phase 4 Study of Enzalutamide

ISN/Protocol 9785-CL-0403

Version 3.1

Incorporating Non-Substantial Amendment 3 [See Attachment 1]

20 October 2016

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Sponsor:

Astellas Pharma Global Development, Inc. (APGD)

1 Astellas Way

Northbrook, IL 60062

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I. SIGNATURES

1. SPONSOR'S SIGNATURES

Required signatures (e.g., protocol author's reviewers and contributors) are located in Section 14, Sponsor's Signatures; e-signatures (when applicable) are located at the end of this document.

2. COORDINATING INVESTIGATOR'S SIGNATURE

A Multicenter, Single-Arm, Open-label, Post-Marketing Safety Study to Evaluate the Risk of Seizure Among Subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Treated with Enzalutamide Who Are at Potential Increased Risk of Seizure (UPWARD)

ISN/Protocol 9785-CL-0403

Version 3.1 / Incorporating Non-Substantial Amendment 3

20 October 2016

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree that it contains all the information required to conduct this study.

Coordinating Investigator:

Signature: .... Date (DD Mmm YYYY)

<Insert name, department/affiliation, name of institution>

Printed Name: .....

Address: .....

.....

3. INVESTIGATOR'S SIGNATURE

A Multicenter, Single-Arm, Open-label, Post-Marketing Safety Study to Evaluate the Risk of Seizure Among Subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Treated with Enzalutamide Who Are at Potential Increased Risk of Seizure (UPWARD)

ISN/Protocol 9785-CL-0403

Version 3.1 / Incorporating Non-Substantial Amendment 3

20 October 2016

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

Principal Investigator:

Signature: _____

Date (DD Mmm YYYY)

Printed Name: _____

Address: _____

_____

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24h-Contact for Serious Adverse Events (SAEs) **See Section 5.5.5**	**Please fax the SAE Worksheet to:** **Astellas Pharma Global Development, Inc.** **Product Safety & Pharmacovigilance** **Fax number: 1-847-317-1241** **Email: Safety-us@us.astellas.com**
Medical Monitor/Experts:	Primary Medical Monitor Contact: PPD , Study Physician PPD Back up Medical Monitor Contact (North America Based) PPD Global Medical Oncology Science PPD
Clinical Research Contacts:	PPD , Global Clinical Science PPD PPD , Global Clinical Science PPD

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
ADT	Androgen Deprivation Therapy
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (GPT)
APGD	Astellas Pharma Global Development
AR	Androgen Receptor
AST	Aspartate Aminotransferase (GOT)
AUC	Area under the curve
AUST	Astellas US Technologies, Inc
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum concentration
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CVA	Cerebrovascular Accident
CYP	Cytochrome P450
DHEA	Dehydroepiandrosterone
DILI	Drug-induced Liver Injury
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EEG	Electroencephalogram
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HR	Hazard Ratio
IAC	Independent Adjudication Committee
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISN	International Study Number
LA-eCRF	Liver Abnormality Electronic Case Report Form
LFT	Liver Function Tests
mCRPC	Metastatic Castration Resistant Prostate Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MRP2	Multidrug Resistance-associated Protein 2
NASH	Non-alcoholic steatohepatitis
PFS	Progression-free Survival
PGx	Pharmacogenomics

Abbreviations	Description of abbreviations
PK	Pharmacokinetic
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SMQ	Standardized MedDRA Query
SOP	Standard Operating Procedure
SRES	Seizure Risk Evaluation Set
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	Total Bilirubin
t_{max}	the time after dosing when C_{max} occurs
ULN	Upper Limit of Normal

Definition of Key Study Terms

Terms	Definition of terms
Baseline	A period that begins at the Screening visit where all initial subject assessments and findings will be obtained prior to study drug administration on Day 1.
Discontinuation	A discontinuation is a subject who is enrolled in the study and for whom study drug is terminated for any reason. Subject will discontinue if he experiences bone disease progression per PCWG2 guidelines, or soft tissue disease progression per RECIST 1.1, the subject initiates treatment with another anticancer therapy, continued dosing would lead to undue risk to the subject in the opinion of the Investigator, subject meets a discontinuation criterion or the Sponsor terminates the study.
Enroll	To enter into the study following the signing of informed consent.
Evaluable subject	Subject with a confirmed seizure (confirmed by the Independent Adjudication Committee) during the 4-month treatment period of the study or who completed at least 3 months (75%) of the planned treatment. Only an enrolled subject who discontinues the study before completing 3 months on treatment may be replaced at the discretion of the Sponsor, however, an enrolled subject who is discontinued due to a confirmed seizure event will not be replaced.
Extension period	Period of time where a subject continues to receive enzalutamide after completing a 4-month treatment period. A subject in the extension period may discontinue for any reasons listed in Discontinuation.
Screening period	30 days prior to Day 1 of Treatment
Screening failure	Screened subject, but did not fulfill protocol inclusion and/or exclusion criteria and failed to receive study treatment, or decided not to participate anymore (withdrew consent) prior to completing pre-treatment period.
Treatment period	Period of time where major interests of protocol objectives are observed, and where the test drug is usually given to a subject which continues until the last assessment after completing administration of the test drug.
Follow-up visit	A visit occurring approximately 30 days following the last dose of enzalutamide or prior to the initiation of another anticancer therapy, whichever comes first.
Subject	An individual who participates in this clinical trial, and will be a recipient of the study drug.
Study period	Period of time from the first site initiation date to the last site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

IV. SYNOPSIS

Date and Version # of Protocol Synopsis:	20 October 2016 / Version 3.1
Sponsor: Astellas Pharma Global Development Inc (APGD)	**Protocol Number:** 9785-CL-0403
Name of Study Drug: Enzalutamide	**Phase of Development:** Phase 4
Title of Study: A Multicenter, Single-arm, Open-Label, Post-Marketing Safety Study to Evaluate the Risk of Seizure Among Subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Treated with Enzalutamide Who Are at Potential Increased Risk of Seizure	
Planned Study Period: From 3Q2013 to 2Q2018	
Study Objective(s): To evaluate the incidence of seizures and monitor the safety of enzalutamide treatment in subjects with metastatic castration-resistant prostate cancer known to have risk factor(s) for seizure	
Planned Total Number of Study Centers and Location(s): Approximately 135 centers; globally	
Study Population: Subjects with metastatic castration-resistant prostate cancer known to have risk factor(s) for seizure	
Number of Subjects to be Enrolled / Randomized: Approximately 400 subjects will be enrolled to achieve a minimum of 350 evaluable subjects assuming a drop-out rate of approximately 13% for this population. In order to avoid patient enrollment being dominated by single patient characteristics in the study, the number of subjects enrolled under each risk factor will be monitored closely. Subjects enrolled under a specific risk category i.e., class of medication may be limited.	
Study Design Overview: This is a multicenter, single-arm, open-label, post-marketing safety study to evaluate the risk of seizure among subjects with metastatic castration-resistant prostate cancer (mCRPC) treated with enzalutamide who are at potential increased risk of seizure. Subjects who meet all inclusion and exclusion criteria will be enrolled into the study and participate in a 4-month treatment period during which once daily dosing of enzalutamide (160 mg/day) will occur, followed by an approximate 30-day follow-up visit for those who do not continue on the extension treatment. At the end of the 4-month treatment visit, subjects who are assessed as deriving benefit from enzalutamide treatment may continue in the extension period where subjects will continue to receive enzalutamide until one of the following criteria is met: 1. The subject experiences bone disease progression per PCWG2 guidelines or soft tissue disease progression per RECIST 1.1, 2. The subject initiates treatment with another anticancer therapy, or continued dosing would lead to undue risk to the subject in the opinion of the Investigator,	

3. The subject meets a discontinuation criterion or
4. The Sponsor terminates this study.

Subjects who are continuing to receive clinical benefit from treatment with enzalutamide and have not met any discontinuation criteria may transition to an open label roll-over extension study upon approval of the study protocol at the institution they are receiving treatment at.

Subjects who meet a discontinuation criterion will be discontinued from enzalutamide therapy 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.

An independent Data Safety and Monitoring Board (DSMB) will monitor seizure data emerging from this study. The DSMB charter will outline the details of the composition and responsibility of the DSMB including early stopping rules.

An Independent Adjudication Committee (IAC) will assess all suspected seizure events occurring during the study. The IAC charter will outline the details of the composition and responsibility of the IAC including classification of those events to be adjudicated and the specification of the event-related documents, listings, data flow, method(s) for data collection, and any applicable data transfers.

Disease assessments will be performed regularly, per standard of care, or when there is clear clinical evidence of progression, while the subject is receiving enzalutamide. Disease assessment will also be performed after a seizure occurs to ensure favorable risk/benefit profile to continue enzalutamide. Disease assessments may include clinical, radiographic and/or PSA assessments.

Inclusion/Exclusion Criteria:

Inclusion:

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 sites in the United States) 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 has histologically confirmed metastatic adenocarcinoma of the prostate.
3. Subject has ongoing androgen deprivation therapy with a GnRH analogue (agonist or antagonist) or bilateral orchiectomy (i.e., surgical or medical castration).
4. Subject has disease progression by at least one of the following:
    a) PSA progression defined by a minimum of 2 rising PSA levels with an interval of at least 1 week between each draw;
    b) Bone disease progression as defined by Prostate Cancer Working Group 2 guidelines (at least 2 new lesions) on bone scan; or
    c) Soft tissue disease progression as defined by RECIST 1.1
5. For subjects who have not had an orchiectomy, there must be a plan to maintain effective GnRH-analogue therapy for the duration of the study.
6. Subject must have failed at least one course of androgen deprivation therapy (ADT), i.e., treatment with GnRH analogues.
7. Subject has an ECOG performance status of 0-2.
8. Subject has been evaluated by a local neurologist prior to study entry who has determined the subject has at least one risk factor for seizure including.
    a) past history of seizure due to any cause except a single febrile seizure in childhood.

Patients with a history of seizures should not have had a seizure within 12 months of Screening and must have had no anticonvulsants for 12 months prior to Screening,
   b) history of cerebrovascular accident (CVA) or transient ischemic attack (TIA),
   c) history of traumatic brain or head injury with loss of consciousness
   d) unexplained loss of consciousness within the last 12 months,
   e) presence of a space occupying lesion in the brain including previously treated brain metastasis(es) or primary CNS tumor,
   f) history of arteriovenous malformations of the brain,
   g) history of brain infection (i.e., abscess, meningitis, or encephalitis),
   h) current use of medication that may lower seizure threshold (see Appendix 12.1),
   i) presence of Alzheimer's disease, meningioma, leptomeningeal disease from prostate cancer.
9. Male subject and his female partner who is of childbearing potential must use two acceptable methods of birth control (one of which must include a condom as a barrier method of contraception) starting at Screening and continuing throughout the study period and for 3 months after final study drug administration.
   a) Two acceptable forms of birth control include:
      i. Condom (barrier method of contraception), AND
      ii. One of the following acceptable forms of contraception is required:
         1. Established use of oral, injected or implanted hormonal methods of contraception.
         2. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
         3. Barrier methods of contraception: Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository).
         4. Vasectomy or surgical castration at least 6 months prior to Screening.
10. Male subject must use a condom, if having sex with a pregnant woman.
11. Male subject must not donate sperm starting at Screening and throughout the study period and for at least 3 months after final drug administration.
12. Subject is able to swallow the study drug and comply with study requirements.
13. Subject agrees not to participate in another interventional study while on treatment.

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

Exclusion:

1. Subject with a history of exposure to enzalutamide.
2. Subject has severe concurrent disease, infection, or co-morbidity that, in the judgment of the Investigator, would make the subject inappropriate for enrollment.
3. Subject is currently being treated with anti-epileptics.
4. Subject has a history of seizure within the past 12 months of Screening as assessed by neurology examination and history.
5. Subject with rapidly progressing visceral disease who has not received and is thought to be able to tolerate cytotoxic chemotherapy. (However, subject who has previously received cytotoxic chemotherapy is permitted).
6. Subject has clinical signs suggestive of high or imminent risks for pathological fracture, spinal cord compression and/or cauda equina syndrome.
7. Subject's absolute neutrophil count is < 1500/μL, platelet count is < 100,000/μL, or

hemoglobin is < 5.6 mmol/L (9 g/dL) at Screening.

8. Subject's total bilirubin is ≥ 1.5 x ULN (except for subjects with documented Gilbert's disease) or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) is ≥ 2.5x ULN at Screening.
9. Subject's estimated creatinine clearance (C_{er}) is less than 30 mL/min by the Cockcroft and Gault formula (Creatinine Clearance (mL/min) = (140 – age)(wt kg) / 72 x serum creatinine (mg/100 ml) [Cockroft, 1976] at Screening.
10. Subject has uncontrolled hypertension as indicated by a resting systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg at Screening.
11. Subject has received an investigational agent within 4 weeks or 5 half- lives whichever is longer prior to Day 1.
12. Subject has shown a hypersensitivity reaction to the active pharmaceutical ingredient or any of the capsule components, including Labrasol, butylated hydroxyanisole, and butylated hydroxytoluene.
13. Subject has any condition which, in the Investigator's opinion, makes the subject unsuitable for study participation.

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

Investigational Product(s):
Enzalutamide

Dose(s):
160 mg once daily

Mode of Administration:
Oral

Enzalutamide Dose Reduction/Dose Adjustment

Subjects who experience a Grade 3 or higher toxicity that is attributed to enzalutamide and cannot be ameliorated by the use of appropriate medical intervention may interrupt treatment with enzalutamide for 1 week or until the toxicity grade improves to Grade 2 or lower severity. Subsequently, study drug dosing may be restarted at the original dose (160 mg/day) or a reduced dose (120 or 80 mg/day) in consultation with the Medical Monitor.

If enzalutamide is co-administered with a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily. If co-administration of strong CYP2C8 inhibitor is discontinued, the enzalutamide dose should return to the dose used prior to initiation of the strong CYP2C8 inhibitor.

If the adverse event is considered not related to enzalutamide by the Investigator, enzalutamide may be resumed at the same dose.

The Sponsor Medical Monitor may be contacted with any questions or concerns on managing dose.

Seizure Therapy:

Standard anticonvulsant measures, if indicated in the event of a seizure (note: concomitant medication restrictions below).

If the decision is made to continue a subject in the study after a first seizure, treatment including anti-seizure medication may be administered as recommended by the local neurologist and guided by the following restrictions. Enzalutamide has the potential to interact with some anti-seizure drugs.

Seizure Therapy continued**:**

- Acceptable drugs unlikely to cause interactions are
  - Levetiracetam
  - Gabapentin
  - Pregabalin
- Drugs which are acceptable but **should be administered with caution** include:
  - Ethosuccimide
  - Lacosamide
  - Lamotrigine
  - Oxcarbazepine
  - Topiramate
  - Valproate
  - Zonisamide
- Benzodiazepines **should not be used** for maintenance therapy of seizure.
- Other anti-seizure medications **not permitted in the study** include:
  - Carbamazepine
  - Phenytoin
  - Phenobarbital
  - Primidone
  - Felbamate
  - Vigabatrin
  - Retigabine

Concomitant Medication Restrictions or Requirements:

The following medications are prohibited during the course of the study:

- Therapies to treat prostate cancer including but not limited to:
  - Cytotoxic chemotherapy
  - Hormonal therapies (e.g., anti-androgens, abiraterone acetate, estrogens; testosterone, dehydroepiandrosterone [DHEA], etc.), 5-alpha reductase inhibitors, ketoconazole;
  - Anticonvulsant substrates of CYP3A4, CYP2C9 or CYP2C19 with a narrow therapeutic index (e.g., carbamazepine, phenytoin, phenobarbital, and primidone);.
- Note: GnRH analogues (agonists or antagonists), bone-targeting agents, such as bisphosphonates and denosumab, and glucocorticoids are allowed. Palliative radiotherapy is also allowed (provided the subject does not meet discontinuation criteria).
- Any other investigational agent.

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) or inducers (e.g. rifampicin) are to be avoided. If subject must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily. If a co-administration of the strong inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.

- Enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Uridine 5'-diphospho-glucuronosyltransferase (UGT1A1) may also be induced. Medicinal products with a narrow therapeutic range that are substrates of CYP3A4, CYP2C9, CYP2C19, or UGT1A1 should be used with caution when administered concomitantly with enzalutamide and may require dose adjustment to maintain therapeutic plasma concentrations as drug levels may be reduced by the interaction with enzalutamide. Such substrates include, but are not limited to:
    - Macrolide antibiotics (e.g. clarithromycin)
    - Benzodiazepines (e.g. diazepam, midazolam, alprazolam, triazolam)
    - Immune modulators (e.g. cyclosporine, tacrolimus)
    - HIV antivirals (e.g. indinavir, ritonavir)
    - Anti-epileptics (e.g. phenobarbital, phenytoin).
    - Coumarins (e.g. warfarin)
- If enzalutamide is co-administered with warfarin (CYP2C9 substrate), additional INR monitoring should be conducted.
- Medicinal products with a narrow therapeutic range that are substrates for P-gp (e.g., digoxin, colchicine, dabigatran etexilate) or for the breast cancer resistant protein (BCRP) or the multidrug resistance-associated protein 2 (MRP2), should be used with caution when administered concomitantly with enzalutamide and may require dose adjustment to maintain optimal plasma concentrations.
- No other new systemic therapy or new radiotherapy for treatment (exception for spinal cord compression, pain management, etc) for prostate cancer is permitted while subject is on the study. Subjects with pre-existing non-target lesions (e.g., bone metastases) receiving palliative radiography for pain treatment before participation in the study are allowed to continue receiving radiotherapy during the study.

Duration of Treatment:

A total of 4 months in duration, starting from the date of the first dose. At the end of the 4-month treatment period, subjects who are assessed as deriving benefit from enzalutamide treatment may continue in the extension period where subjects will continue to receive enzalutamide until one of the following criteria is met:

1. The subject experiences bone disease progression per PCWG2 guidelines or soft tissue disease progression per RECIST 1.1,
2. The subject initiates treatment with another anticancer therapy, continued dosing would lead to undue risk to the subject in the opinion of the Investigator,
3. The subject meets a discontinuation criterion or
4. The Sponsor terminates the study.

The total study drug treatment duration for the extension period will depend on individual clinical benefit with enzalutamide treatment as assessed by the Investigator.

Subjects may be asked to complete their extension period participation in another Astellas sponsored study upon activation of the roll-over extension study at the institution.

Discontinuation Criteria:

The following safety/compliance events will result in the removal of subjects from enzalutamide therapy and from the study, if:

- Any adverse event that is intolerable to the subject and that cannot be ameliorated by the use of adequate medical intervention, or that in the opinion of the Investigator would lead to undue risk to the subject if dosing continued;
- Any first confirmed seizure requiring treatment with maintenance anticonvulsant therapy if the only anticonvulsant(s) the patient can tolerate is carbamazepine, phenytoin, phenobarbital, primidone, felbamate, vigabatrin, or retigabine.
- Any second seizure confirmed by the independent Adjudication Committee;
- Inability to maintain the absolute neutrophil count above 500/µL (Grade 4) or 500-1000/µL (Grade 3) with evidence of infection;
- Inability to maintain the platelet count above 25,000/µL (Grade 4) or 25,000-50,000/µL (Grade 3) with spontaneous bleeding;
- Subject who has unequivocal evidence of disease progression (upon bone disease progression per PCWG2 guidelines or soft tissue disease progression per RECIST 1.1) or, is no longer deriving clinical benefit;
- Subject who is, in the opinion of the Investigator or the Medical Monitor, grossly non-compliant with the protocol requirements.

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

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks (in subjects without liver metastases
- ALT or AST > 3 × ULN and TBL > 2 × ULN or INR > 1.5 (If INR testing is applicable/evaluated)
- ALT or AST > 5 × ULN and (TBL > 2 × ULN in patients with liver metastases)

● ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).
Formal Stopping Rules The study design considers early stopping criteria that can be applied to a study as a whole or a specific risk factor group, if any, based on the statistical boundary calculated from Maximized Sequential Probability Ratio Test [Kulldorff, 2011]. The statistical boundary will be provided in the DSMB charter. Evaluation of the seizure risk is performed by DSMB for the study as a whole and for the risk factor group at the same time using the same stopping boundary based on false stopping probability of 0.1. Recommendation will be made by DSMB to either stop the study or stop further enrollment of a specific risk factor group.
Endpoints for Evaluation: Primary: The proportion of evaluable subjects with at least one confirmed seizure as adjudicated by the Independent Adjudication Committee (IAC) during the 4-month treatment duration. Secondary: Not applicable Exploratory: Not applicable

Suspected Seizure Event Management:

Each subject will be given a patient card with the following information; a list of signs and symptoms of a suspected seizure (Seizure Description Subject Information) and a Suspected Seizure Event Questionnaire list as well as instructions regarding what to do in the event of a suspected seizure for awareness.

The subject will contact the Investigator immediately (within 24 hours) after onset of a suspected seizure event and return to the site with best efforts in 3 days after event for evaluation by the local neurologist.

Investigator will:

- Instruct the subject to stop taking the enzalutamide study drug until after the clinical assessment has been completed by the neurologist. (Note: this could be a temporary stoppage, if the event turns out not to have been deemed a seizure, or is a 1st seizure with good benefit/risk ratio for continuing study drug.)
- Instruct the subject to complete the Suspected Seizure Event Questionnaire with input from any witness(es) to suspected events.
- Schedule a clinic visit to be evaluated by the local neurologist.

Evaluation by a local neurologist is required including electroencephalogram (EEG) and magnetic resonance imaging (MRI of the brain) procedures as soon as possible after a potential seizure event occurrence. A description of the events leading up to the seizure will be obtained from the individual and any witnesses.

The study site will interview the subject and any witnesses, if possible, regarding the event. The study site will complete a Suspected Seizure Event Questionnaire including a Cover Sheet which will be signed by the PI/Sub-Investigator and be included as part of the package to the IAC. The site will review the Suspected Seizure Event Questionnaire completed by the subject, if available. The subject Suspected Seizure Event Questionnaire is a tool to capture information of the suspected event which the PI/Sub-Investigator will utilize for completion of their evaluation when available. The Questionnaire completed by the subject will not be collected.

Subjects will be treated as indicated by the local neurologist including the use of acceptable anti-convulsants Anticonvulsant substrates of CYP3A4, CYP2C9 or CYP2C19 with a narrow therapeutic index are **not** permitted (e.g., anticonvulsant medications including carbamazepine, phenytoin, phenobarbital, primidone, felbamate, vigabatrin, and retigabine).

If the treating neurologist deems the event not to have been a seizure, enzalutamide may be restarted. If the neurologist determines that a seizure has occurred and the event is a first seizure, prior to the IAC assessment, an allowable anticonvulsant may be administered on a maintenance basis and enzalutamide may be restarted if desired by the investigator and subject, AFTER confirmation of clinical benefit as assessed by the Investigator. Results of the assessment of the IAC will be provided to the investigator and the subject will be allowed to continue in the study if the event is determined to be a first confirmed seizure.

In the event of a second seizure, enzalutamide will be held until the IAC's review is completed. Upon IAC confirmation of a second seizure, enzalutamide may not be restarted and the subject will be discontinued from the study.

All relevant information, including the completed seizure assessment questionnaire, the neurologist's evaluation, and results of the MRI of the brain and EEG, will be submitted to the IAC for evaluation. Results of the assessment of the IAC will be provided to the investigator and the subject will be allowed to continue in the study if the event is determined to be a first confirmed seizure. If the seizure is determined by the IAC to be a second confirmed seizure event in the study,

the subject will be withdrawn from the study. If it is determined that the event did not meet criteria for a confirmed seizure, the subject can continue in the study if no other discontinuation criteria have been met.

DSMB and IAC

A DSMB will be established for this study and remain active for the study duration. The DSMB will examine safety data and be informed of seizure events as expediently as possible. The role and responsibilities of the DSMB will be described in the DSMB charter which will be in place for the start of the study. Details of statistical boundaries for monitoring of the seizure event will be provided in the DSMB charter.

An IAC will be established to assess all suspected seizure events occurring during the study. The committee will consist of independent members of appropriate expertise who are not directly involved in the conduct of the clinical study. Suspected seizure adverse events and related information of the cases will be sent to the committee for assessment. The IAC charter will describe the classification of those events to be adjudicated and the specification of the event-related documents, listings, data flow, method(s) for data collection, and any applicable data transfers.

Statistical Methods:

Sample size justification:

Approximately four hundred (400) subjects will be enrolled to target approximately 350 evaluable subjects assuming an early discontinuation of study drug of approximately 13% for this population and based on the recommendation from the FDA, respectively. Assuming the true incidence of seizure in the first 4 months as 0.9%, based on the incidence rate of 2.8 per 100 patient years, which is obtained from the previous studies and the sample size of 350, the chance of observing 5 or less subjects with seizure events is 88.9%. Given 5 out of 350 subjects, i.e., point estimate of 1.43%, the upper limit 95% exact confidence interval will be 3.31% and the width of the exact confidence interval will be 2.84%.

Efficacy:

Efficacy data will be listed.

Pharmacokinetics:

Not applicable

Pharmacodynamics:

Not applicable

Safety:

An evaluable subject is defined as a subject with a confirmed seizure during the 4-month treatment period of the study or who completed at least 3 months (75%) of the treatment. Only an enrolled subject who discontinues the study before completing 3 months on treatment may be replaced at the discretion of the Sponsor, however, an enrolled subject who is discontinued due to a confirmed seizure event will not be replaced.

Primary endpoint, the proportion of evaluable subjects with at least one confirmed seizure as adjudicated by the IAC during the 4-month treatment duration, will be estimated using a point estimate and its 95% exact confidence interval.

In addition, a cumulative summary to include all seizure events, including those occurring beyond the 4 month-treatment period, will be reported using all evaluable subjects. Seizures will continue

to be monitored for subjects entering the extension study.

A data-cut off for a cumulative summary will be one year after the primary 4-month treatment visit. For any subject who continues on treatment after his 1 year extension period, data collection will be limited to dosing information, and all AEs including serious adverse events (SAEs).
All other safety analyses will include subjects who receive at least one dose of enzalutamide (safety population).

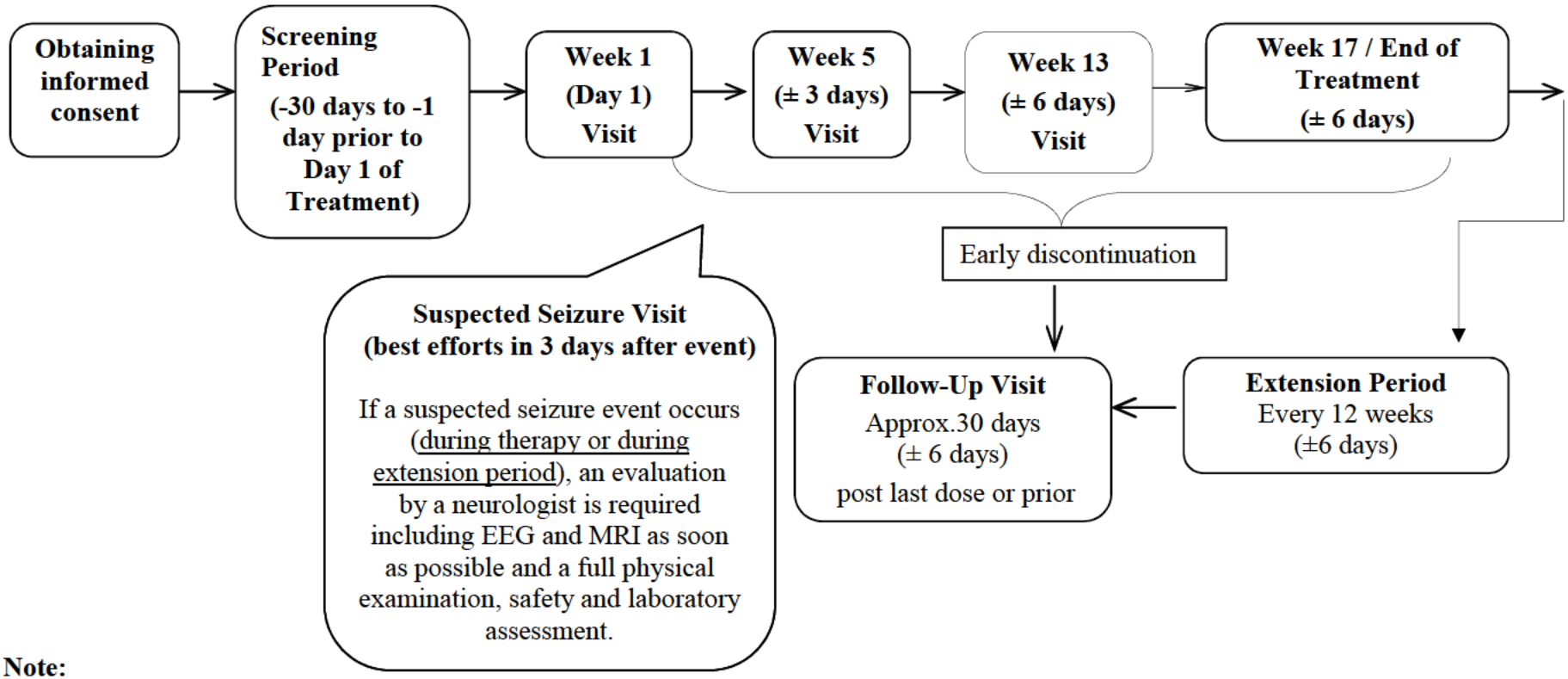
All adverse events will be coded to preferred term, higher level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and proportion of subjects with adverse events will be presented by MedDRA system organ class and preferred term, relationship to enzalutamide, and severity. Laboratory values will be classified as applicable by the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) severity grade (version 4.03). Laboratory shift tables of the baseline results to the worst values will be produced.

Interim analyses:

No formal interim analysis is planned for a specific timepoint.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart



Note:

- Disease assessments should be performed regularly, per standard of care, or when there is clear clinical evidence of progression, while the subject is receiving enzalutamide. Disease assessments must also be performed after a first confirmed seizure to ensure a favorable risk/benefit profile in the event the patient wishes to continue enzalutamide (requiring maintenance anticonvulsant therapy).

A 2nd confirmed seizure mandates discontinuation.

Table 1 Schedule of Assessments

Assessments	Screening Period (-30 days to – 1 day prior to Day 1 of Treatment)	Treatment Period					Extension Period [j]	Follow-up Visit [b]
		Week 1 Day 1 (n/a)	Week 5 (± 3 days)	Week 13 (± 6 days)	Week 17/End of Treatment (±6 days)	Suspected Seizure Visit [c] (best efforts in 3 days after event)	Every 12 weeks (±6 days)	Approx.30 days (± 6 days) post last dose or prior to start of another anticancer therapy
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Upon occurrence	--	--
Informed Consent [a]	X							
Verify Inclusion/Exclusion	X							
Medical History	X							
Prostate Cancer History	X							
Demographics	X							
ECOG Performance Status	X							
Vital Signs (Blood Pressure, Heart Rate and Temperature)	X	X	X	X	X		X	X
Physical Examination [d]	X	X	X	X	X		X	X
Neurologist Examination [e]	X							
Weight and Height	X							
Clinical Labs [f]	X	X	X	X	X	X	X	X
12-Lead ECG	X			X	X	X		X
Blood Sample Collection for PGx Analysis	X							
Evaluation by a Neurologist, MRI, EEG						X		
Seizure Event Questionnaire [g]						X		
Disease Assessments [h]	X			X	X[h]	X	X	X
Adverse Events	X[i]	X	X	X	X	X	X	X
Concomitant Medications	←							→
Enzalutamide Dispensing		X	X		X [k]		X	

Footnotes appear on next page

a. Informed consent form must be obtained prior to any study-specific procedures being performed.
b. A Follow-up Visit will be performed approximately 30 days after the last dose of enzalutamide, or prior to the initiation of another anticancer therapy, whichever occurs first.
c. Suspected seizure visit occurring any time during the 4 month therapy as well as during extension period.
d. Full physical exams will be performed including neurological exam. The physical examination performed at the Screening Visit does not need to be repeated on Day 1, if the Day 1 visit occurs within 72 hours of Screening.
e. At Screening, a thorough neurological history and examination will be performed by a local neurologist to obtain complete medical history relating to seizure risk, to confirm that a subject has met seizure risk entry criteria and to complete neurological baseline examination.
f. The laboratory assessments performed at the Screening visit do not need to be repeated on Day 1, if the Day 1 visit occurs within 72 hours of Screening.
g. This is the Questionnaire to be completed both by Subject (if available) and by PI/Sub-investigator. The Questionnaire completed by the subject will not be collected.
h. Disease assessments will be performed regularly, per standard of care, or when there is clear clinical evidence of progression, while the subject is receiving enzalutamide. Disease assessments will also be performed after a first confirmed seizure to ensure favorable risk/benefit profile to continue enzalutamide. Disease assessments may include clinical, radiographic and/or PSA assessments. The method Investigator uses for disease assessment must remain constant throughout the study. Radiographic disease assessments performed at Week 13 (Visit 4) do not need to be repeated at Week 17/End of Treatment (Visit 5).
i. Serious adverse events (SAEs) including death will be collected from the time the subject signs the consent form until 30 days after last dose of enzalutamide. Non-serious adverse events will be collected from time of study drug administration on Day 1 until 30 days after last dose of enzalutamide.
j. Extension period will begin for subjects who are assessed as deriving benefit from enzalutamide treatment after completion of the 4-month treatment. For any subject who continues on treatment after his 12-month extension period, data collection will be limited to dosing information, concomitant medication, and all AEs including SAEs. Subjects continuing into the Extention period may be asked to complete their extension period participation in another Astellas sponsored study upon activation of the roll-over extension study at the institution. A Follow-up visit will not be required if subject move into the roll-over extension study.
k. For only subjects continuing in the extension period who do not continue into the roll-over extension study at the institution.

1 INTRODUCTION

1.1 Background

Enzalutamide (formerly MDV3100) is an androgen receptor (AR) inhibitor that blocks multiple steps in the AR signaling pathway. Enzalutamide competitively inhibits binding of androgens to ARs, inhibits nuclear translocation of receptors and inhibits the association of the AR with DNA even in the setting of AR over expression and in prostate cancer cells resistant to anti-androgens. By inhibiting AR signaling, enzalutamide elicits several downstream effects, which include reduced expression of AR-dependent genes, decreased growth of prostate cancer cells, induction of cancer cell death, and tumor regression. Enzalutamide lacks agonist activities such as those that may limit the sustained efficacy of current anti-androgens.

In the Phase 3 study CRPC2 (AFFIRM), the prespecified interim analysis at the time of 520 events demonstrated a statistically significant improvement in overall survival in patients with metastatic CRPC treated with enzalutamide versus placebo (hazard ratio [HR] = 0.631; 95% CI: 0.529, 0.752, $p < 0.0001$). Median survival was 18.4 months in the enzalutamide arm and 13.6 months in the placebo arm ($\Delta = 4.8$ months).

In the AFFIRM study, 7 of 800 (0.9%) patients treated with enzalutamide 160 mg once daily experienced a seizure. No seizures occurred in patients treated with placebo. Seizures occurred from 31 to 603 days after initiation of enzalutamide. Patients experiencing seizure were permanently discontinued from therapy and all seizures resolved.

This study is being conducted to assess the risk of seizure in patients with characteristics that were previously excluded from clinical studies and to monitor the safety of enzalutamide in patients with metastatic castration-resistant prostate cancer who are known to have risk factor(s) for seizure. Although no direct comparison is planned in this study, the results from the study will be interpreted in the context of all available data on enzalutamide and seizure risk in the general patient population and available epidemiological data at the timing of study reporting.

1.2 Non-clinical and Clinical Data

1.2.1 Summary of Relevant Nonclinical Experience with Enzalutamide

A complete assessment of toxicity has been conducted with enzalutamide, including evaluation of impurities. The species included in the toxicity program were mice, rats, dogs, and cynomolgus monkeys. Toxicokinetic evaluations demonstrated that all of these species produce the 2 major human metabolites of enzalutamide, N-desmethyl enzalutamide and an inactive carboxylic acid derivative.

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of enzalutamide.

Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either the in vitro cytogenetic assay with mouse lymphoma thymidine kinase gene mutation or the in vivo mouse micronucleus assay.

In a cell-based activity assay both enzalutamide (formerly MDV3100) and its active metabolite functionally inhibited the GABA-gated chloride channel (α1β3 and α1β3γ2 GABA-A receptor subtype). In addition enzalutamide treatment was associated with dose-dependent convulsions in mice, and convulsions were also observed in 1 rat and 2 dogs in repeat dose toxicity studies. Both enzalutamide and its active metabolite cross the blood-brain barrier, and comparison of brain concentrations of these compounds in mice with and without convulsions shows that seizurogenic activity is mainly dependent on the extent of brain penetration.

Additional information on the nonclinical experience with enzalutamide is provided in the Enzalutamide Investigator Brochure.

1.2.2 Summary of Relevant Clinical Experience with Enzalutamide

The key clinical studies evaluating enzalutamide in men with prostate cancer are described briefly as follows:

S-3100-1-01: The pharmacokinetics (PK), tolerability, and antitumor activity of enzalutamide (then known as MDV3100) were first studied in a multicenter, open-label, first-in-human, dose-escalation study in 140 patients with CRPC. Patients who were chemotherapy-naïve or who had previous docetaxel-based chemotherapy failure were treated with enzalutamide at doses of 30 to 600 mg/day until disease progression or intolerable side effects developed. The maximum tolerated dose was determined to be 240 mg daily. After review of all data available from S-3100-1-01, the optimal dose of enzalutamide for evaluation in Phase 3 clinical trials was determined to be 160 mg/day.

CRPC2 (AFFIRM): A multinational Phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study of enzalutamide (160 mg daily) in patients with progressive CRPC previously treated with docetaxel-based chemotherapy was conducted in 1199 men, 800 of whom received treatment with enzalutamide. The primary endpoint was overall survival. The FDA and EU approval of enzalutamide was based on the results of this study.

MDV3100-03 (PREVAIL): A multinational, Phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study of enzalutamide (160 mg daily) in chemotherapy-naïve patients with progressive metastatic prostate cancer who have failed androgen deprivation therapy is ongoing. Enrollment is complete with 1717 men, approximately half of whom received treatment with enzalutamide. The coprimary endpoints are overall survival (OS) and radiographic progression-free survival (PFS).

1.2.2.1 Pharmacokinetics and Drug Metabolism

In PK investigations in men with CRPC, enzalutamide was absorbed rapidly after oral administration, with the time to maximum plasma concentration (t_{max}) after a single dose typically occurring at 1 hour post dose. No major deviations from dose proportionality were observed over the dose range 30 mg to 600 mg.

Terminal half-life was approximately 5.8 days. The average difference between the peak (maximum plasma concentration, C_{max}) and trough (predose plasma concentration, C_{trough}) concentrations was ≤ 25%. Therefore, plasma profiles at steady state resembled a constant

infusion. Time-liner PK was observed beyond steady state at Day 28. Plasma concentrations of enzalutamide and the active metabolite, N-desmethyl enzalutamide, were approximately the same.

In a drug-drug interaction study in male patients with CRPC (9785-CL-0007), a single oral dose of a substrate for cytochrome P450 (CYP) 2C8, CYP2C9, CYP2C19, or CYP3A4 was administered before and concomitantly with enzalutamide (after at least 55 days of dosing at 160 mg daily). Enzalutamide at steady state reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate) by 86%, 56%, and 70%, respectively. Based on the magnitude of the decreases in exposure, enzalutamide is considered a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Substrates of CYP3A4, CYP2C9, and CYP2C19 with a narrow therapeutic index should be avoided when possible, as enzalutamide may decrease plasma exposure of these drugs. If enzalutamide is coadministered with warfarin (CYP2C9 substrate), additional international normalized ratio (INR) monitoring should be conducted. Enzalutamide did not cause clinically meaningful changes in exposure to pioglitazone (CYP2C8 substrate).

In a drug-drug interaction study in healthy male volunteers (9785-CL-0006), a single 160 mg oral dose of enzalutamide was administered alone or after multiple oral doses of gemfibrozil (strong CYP2C8 inhibitor). Gemfibrozil increased the composite area under the curve from time zero to infinity ($AUC_{0-\infty}$) of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold with minimal effect on C_{max}; therefore, strong CYP2C8 inhibitors should be avoided when possible as they can increase plasma exposure to enzalutamide plus N-desmethyl enzalutamide. If coadministration with a strong CYP2C8 inhibitor is necessary, the dose of enzalutamide should be reduced to 80 mg once daily. If coadministration of the strong CYP2C8 inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor. The effects of CYP2C8 inducers on the PK of enzalutamide have not been evaluated in vivo.

In the drug-drug interaction study in healthy male volunteers (9785-CL-0006), a single 160 mg oral dose of enzalutamide was administered alone or after multiple oral doses of itraconazole (strong CYP3A4 inhibitor). Itraconazole increased the composite $AUC_{0-\infty}$ of enzalutamide plus N-desmethyl enzalutamide by 1.3-fold with no effect on C_{max}. As this small change is not clinically meaningful, no starting dose adjustment is needed when coadministering enzalutamide with CYP3A4 inhibitors. The effects of CYP3A4 inducers on the PK of enzalutamide have not been evaluated in vivo.

Additional information on the PK and drug metabolism of enzalutamide is provided in the Enzalutamide Investigator Brochure.

1.3 Summary of Key Safety Information for Enzalutamide

The most common adverse reactions (≥ 5%) in patients treated with enzalutamide (N = 800) in the Phase 3 study CPRC2 (AFFIRM) (N = 1199) were asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection,

spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension. Discontinuations due to adverse events were reported for 16% of enzalutamide-treated patients and 18% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the enzalutamide-treated patients and none (0%) of the placebo-treated patients.

Seizure is an identified risk associated with enzalutamide, based on nonclinical findings, the results of the dose-escalation study in patients with CRPC, S-3100-1-01, and events observed in subsequent clinical trials. In Study S-3100-1-01, seizures were reported in 3 patients and identified as dose-limiting toxicities (DLTs), 1 each at daily doses of 360, 480 and 600 mg enzalutamide. No seizures were reported in patients receiving daily doses of 240 mg enzalutamide or below in this study. Given the potential risk of seizure associated with enzalutamide, investigators were instructed to have a heightened vigilance for seizures or any events suggesting seizure activity in the controlled Study CRPC2 and all subsequent studies.

In the randomized clinical trial CRPC2, 7 of 800 (0.9%) patients treated with enzalutamide 160 mg once daily experienced a seizure. No seizures occurred in patients treated with placebo. The onset of seizure events ranged from 31 to 603 days after initiation of enzalutamide. Patients experiencing seizure were permanently discontinued from enzalutamide therapy and all seizures resolved. There is no clinical trial experience re-administering enzalutamide to patients who experienced seizures. The safety of enzalutamide in patients with predisposing factors for seizure is not known because these patients were excluded from the trial. These exclusion criteria included a history of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within the previous 12 months, cerebral vascular accident, brain metastases, brain arteriovenous malformation or the use of concomitant medication that may lower the seizure threshold.

As of the cutoff date of 01Jan 2014, seizure occurred in <1% of prostate cancer patients receiving enzalutamide who previously received docetaxel (chemotherapy), and < 0.1% of prostate cancer patients receiving enzalutamide who had not received chemotherapy.

1.4 Risk-Benefit Assessment

In the Phase 3 study CRPC2 (AFFIRM), the pre-specified interim analysis at the time of 520 events demonstrated a statistically significant improvement in overall survival in patients with metastatic CRPC treated with enzalutamide versus placebo (hazard ratio [HR] = 0.631; 95% CI: 0.529, 0.752, $p < 0.0001$). Median survival was 18.4 months in the enzalutamide arm and 13.6 months in the placebo arm ($\Delta = 4.8$ months). The overall survival benefit was consistent across all subgroups, including age, baseline pain intensity, geographic region, and type of disease progression at entry. Enzalutamide treatment was superior to placebo for all secondary endpoints including proportion of patients with a reduction in PSA level by 50% or more (54% vs. 2%, $p < 0.001$), soft tissue response rate (29% vs. 4%, $p < 0.001$), quality-of-life response rate (43% vs. 18%, $p < 0.001$), time to PSA progression (8.3 vs. 3.0 months; HR 0.25, $p < 0.001$), radiographic PFS (8.3 vs. 2.9 months; HR 0.40, $p < 0.001$), and time to first skeletal-related event (16.7 vs. 13.3 months; HR 0.69, $p < 0.001$). Based on

the AFFIRM data, the US FDA approved enzalutamide in August 2012 for men with metastatic CRPC who previously received docetaxel therapy.

Review of the enzalutamide program safety information obtained through Jan 2014 confirmed that the previously identified potential risk of seizure is an "important identified risk" per International Conference on Harmonisation (ICH) definition, with an estimated incidence of <1% based on cumulative data. In addition to seizures, hypertension, falls, hallucinations, non-pathologic fractures, neutrophil count decrease, and Cognitive/memory impairment were defined as important identified risks

The confirmed benefit of enzalutamide in the randomized CRPC2 trial in terms of overall survival advantage over placebo indicates a favorable benefit risk profile even in patients who were systematically excluded from clinical studies and may be at potential increased risk of seizure described in this protocol.

This study will enroll metastatic CRPC patients who have at least one risk factor which has the potential to increase risk for seizure. All subjects will have a baseline neurology assessment prior to treatment initiation with enzalutamide.

This study will have an independent DSMB to monitor the safety, including being informed of every seizure event occurring during the trials as well as the assessment from the IAC as to whether the event actually qualifies as a seizure.

2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

2.1 Study Objective

The study objective is to evaluate the seizure rate and monitor the safety of enzalutamide treatment in subjects with metastatic castration-resistant prostate cancer known to have risk factor(s) for seizure.

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This study is being conducted to assess the risk of seizure in patients with characteristics that were previously excluded from clinical studies and to monitor the safety of enzalutamide in patients with metastatic castration-resistant prostate cancer who are at potential increased risk of seizure.

Seizure is an identified important risk and known toxicity of enzalutamide, based on nonclinical findings and the results of the dose-escalation study in patients with castration resistant prostate cancer (S-3100-1-01) and the AFFIRM study (CRPC2). However, it needs to be noted that the exact mechanism by which enzalutamide may lower the seizure threshold is not known, but could be related to the affinity of enzalutamide and the metabolite M2 for the GABA-gated chloride channel.

Risk factors that could contribute to the risk of seizure were excluded in the ongoing and closed studies; however, some risk factors were unknowingly present in several patients which may have independently increased their risk of seizure (i.e., brain metastasis).

The current study will assess to the best of the current knowledge, the risk of seizure in a patient population at risk, with the potential limitation that not all factors that could contribute to that risk may be known or identified. Additionally, this study does not include a comparator arm, therefore any comparison to other drugs used in that indication will be indirect and only reflect the published literature. One additional limitation is that the study population may also not entirely reflect the patient population at potential risk as there are other inclusion/exclusion criteria that determine enrollment.

This trial has been designed to analyze the incidence of seizure in the presence of potential risk factors. This approach will lead to reducing the potential bias which can be caused by dominating risk factor(s). However, there may be a situation where very few patients are enrolled with a particular risk factor making estimation of seizure incidence associated with that risk factor not feasible.

This is a multicenter, single-arm, open-label, post-marketing safety study to evaluate the risk of seizure among subjects with metastatic castration-resistant prostate cancer (mCRPC) treated with enzalutamide who are at potential increased risk of seizure.

Eligible patients may be drawn from various sources including hospitals and private practices of urologists and oncologists, and community based organizations where patients will be screened for the eligibility criteria of the study.

Subjects who meet all inclusion and exclusion criteria will be enrolled into the study and participate in a 4-month treatment period during which once daily dosing of enzalutamide (160 mg/day) will occur followed by an approximate 30-day follow-up visit for those who do not continue on the extension treatment or prior to the initiation of another anticancer therapy, whichever occurs first.

At the end of the 4-month treatment visit, subjects who are assessed as deriving benefit from enzalutamide treatment may continue in the extension period where subjects will continue to receive enzalutamide until one of the following criteria is met:

1. The subject experiences bone disease progression per PCWG2 guidelines or soft tissue disease progression per RECIST 1.1,
2. The subject initiates treatment with another anticancer therapy, or continued dosing would lead to undue risk to the subject in the opinion of the Investigator,
3. The subject meets a discontinuation criterion or,
4. The Sponsor terminates this study.

Subjects who are continuing to receive clinical benefit from treatment with enzalutamide and have not met any discontinuation criteria may transition to an open label roll-over extension study upon approval of the study protocol at the institution they are receiving treatment.

Subjects who do not continue in the extension period or who meet a discontinuation criterion will be discontinued from enzalutamide therapy 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.

When any subject who continues on treatment after his 12-month extension period, data collection will be limited to dosing information, concomitant medications, and all AEs including serious adverse events (SAEs).

Each subject will be given a patient card with the following information; a list of signs and symptoms of a suspected seizure (Seizure Description Subject Information) and a Suspected Seizure Event Questionnaire list as well as instructions regarding what to do in the event of a suspected seizure for awareness.

The subject will contact the Investigator immediately (within 24 hours) after onset of a suspected seizure event and return to the site with best efforts in 3 days after event for evaluation by the local neurologist.

Investigator will:

- Instruct the subject to stop taking the enzalutamide study drug until after the clinical assessment has been completed by the neurologist. (Note: this could be a temporary stoppage, if the event turns out not to have been deemed a seizure, or is a 1st seizure with good benefit/risk ratio for continuing study drug.)
- Instruct the subject to complete the Suspected Seizure Event Questionnaire with input from any witness(es) to suspected events.
- Schedule a clinic visit to be evaluated by the local neurologist.

Evaluation by a local neurologist is required including electroencephalogram (EEG) and magnetic resonance imaging (MRI of the brain) procedures as soon as possible after a potential seizure event occurrence. A description of the events leading up to the seizure will be obtained from the individual and any witnesses.

The study site will interview the subject and any witnesses, if possible, regarding the event. The study site will complete a Suspected Seizure Event Questionnaire including a Cover Sheet which will be signed by the PI/Sub investigator and included as part of the package to the IAC. The site will review the Suspected Seizure Event Questionnaire completed by the subject, if available. The subject Suspected Seizure Event Questionnaire is a tool to capture information of the suspected event which the PI/Sub-investigator will utilize for completion of their evaluation when available. The Questionnaire completed by the subject will not be collected.

Subjects will be treated as indicated by the local neurologist including acceptable anti-convulsants, if indicated.

If the treating neurologist deems the event not to have been a seizure, enzalutamide may be restarted.

If the neurologist determines that a seizure has occurred and the event is a first seizure prior to the IAC assessment, an allowable anticonvulsant may be administered on a maintenance basis and enzalutamide may be restarted if desired by the investigator and subject, AFTER confirmation of clinical benefit as assessed by the Investigator. Results of the assessment of the IAC will be provided to the investigator and the subject will be allowed to continue in the study if the event is determined to be a first confirmed seizure.

In the event of a second seizure, enzalutamide will be held until the IAC's review is completed. Upon IAC confirmation of a second seizure, enzalutamide may not be restarted and the subject will be discontinued from the study.

All relevant information, including the completed seizure assessment questionnaire, the local neurologist's evaluation, and results of the MRI of the brain and EEG, will be submitted to the IAC for evaluation. Results of the assessment of the IAC will be provided to the Investigator and the subject will be allowed to continue in the study if the event is determined to be a first confirmed seizure. If the seizure is determined by the IAC to be a second confirmed seizure event, the subject will be withdrawn from the study. If it is determined that the event did not meet criteria for a confirmed seizure, the subject can continue in the study if no other discontinuation criteria have been met.

Disease assessments should be performed regularly per standard of care or when there is clear clinical evidence of progression, while the subjects are receiving enzalutamide and also upon confirmation of a first seizure to confirm clinical risk/benefit profile to continue enzalutamide.

2.2.2 Dose Rationale

A dose of 160 mg enzalutamide (four 40 mg capsules) once daily administered orally is the recommended daily dose by regulatory agencies in countries where the drug has been approved.

2.3 Endpoints

2.3.1 Primary Endpoints

The proportion of evaluable subjects with at least one confirmed seizure as adjudicated by the Independent Adjudication Committee (IAC) during the 4-month treatment duration.

An evaluable subject is defined as a subject with a confirmed seizure during the 4-month treatment period of the study or who completed at least 3 months (75%) of the planned treatment. Only an enrolled subject who discontinues the study before completing 3 months on treatment may be replaced at the discretion of the Sponsor, however, an enrolled subject who is discontinued due to a confirmed seizure event will not be replaced.

A cumulative summary to include all seizure events, including those occurring beyond the 4 month treatment period will be included.

In case the drop-out rate is higher than expected, appropriate method such as Kaplan-Meier estimations may be considered.

2.3.2 Secondary Endpoints

Not applicable.

2.3.3 Exploratory Endpoints

Not applicable.

3 STUDY POPULATION

3.1 Selection of Study Population

The study population will include approximately 400 men with metastatic castration-resistant prostate cancer known to have risk factor(s) for seizure.

In order to avoid patient enrollment being dominated by single patient characteristics in the study, the number of subjects enrolled under each risk factor will be monitored closely. Subjects enrolled under a specific risk category i.e., class of medication may be limited.

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 (HIPAA) 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 has histologically confirmed metastatic adenocarcinoma of the prostate.
3. Subject has ongoing androgen deprivation therapy with a GnRH analogue (agonist or antagonist) or bilateral orchiectomy (i.e., surgical or medical castration).
4. Subject has disease progression by at least 1 of the following:
    a) PSA progression defined by a minimum of 2 rising PSA levels with an interval of at least 1 week between each draw;
    b) Bone disease progression as defined by Prostate Cancer Working Group 2 guidelines (at least 2 new lesions) on bone scan; or
    c) Soft tissue disease progression as defined by RECIST 1.1
5. For subjects who have not had an orchiectomy, there must be a plan to maintain effective GnRH-analogue therapy for the duration of the study.
6. Subject must have failed at least one course of androgen deprivation therapy (ADT), i.e., treatment with GnRH analogues.
7. Subject has an ECOG performance status of 0-2.
8. Subject has been evaluated by a local neurologist prior to study entry who has determined the subject has at least one risk factor for seizure including:

a) past history of seizure due to any cause except a single febrile seizure in childhood. Patients with a history of seizures should not have had a seizure within 12 months of Screening and must have had no anticonvulsants for 12 months prior to Screening.
b) history of cerebrovascular accident (CVA) or transient ischemic attack (TIA),
c) history of traumatic brain or head injury with loss of consciousness,
d) unexplained loss of consciousness within the last 12 months,
e) presence of a space occupying lesion in the brain including previously treated brain metastasis(es) or primary CNS tumor,
f) history of arteriovenous malformations of the brain,
g) history of brain infection (i.e., abscess, meningitis, or encephalitis),
h) current use of medication that may lower seizure threshold (see Appendix 12.1),
i) presence of Alzheimer's disease, meningioma, leptomeningeal disease from prostate cancer.

9. Male subject and his female partner who is of childbearing potential must use two acceptable methods of birth control (one of which must include a condom as a barrier method of contraception) starting at Screening and continuing throughout the study period and for 3 months after final study drug administration.
    a) Two acceptable forms of birth control include:
        i. Condom (barrier method of contraception), AND
        ii. One of the following acceptable forms of contraception is required:
            1. Established use of oral, injected or implanted hormonal methods of contraception.
            2. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
            3. Barrier methods of contraception: Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository).
            4. Vasectomy or surgical castration at least 6 months prior to Screening.
10. Male subject must use a condom, if having sex with a pregnant woman.
11. Male subject must not donate sperm starting at Screening and throughout the study period and for at least 3 months after final drug administration.
12. Subject is able to swallow the study drug and comply with study requirements.
13. 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 with a history of exposure to enzalutamide.
2. Subject has severe concurrent disease, infection, or co-morbidity that, in the judgment of the Investigator, would make the subject inappropriate for enrollment.
3. Subject is currently treated with anti-epileptics.

4. Subject has a history of seizure in the past 12 months of Screening as assessed by neurology examination and history.
5. Subject with rapidly progressive visceral disease who has not received and is thought able to tolerate cytotoxic chemotherapy. (However, subject who has previously received cytotoxic chemotherapy is permitted).
6. Subject has clinical signs suggestive of high or imminent risks for pathological fracture, spinal cord compression and/or cauda equina syndrome.
7. Subject's absolute neutrophil count is < 1500 /μL, platelet count is < 100,000/μL, or hemoglobin is < 5.6 mmol/L (9 g/dL) at Screening.
8. Subject's total bilirubin is ≥ 1.5 x ULN (except for subjects with documented Gilbert's disease) or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) is ≥ 2.5x ULN at Screening.
9. Subject's estimated creatinine clearance (C_{er}) is less than 30 mL/min by the Cockcroft and Gault formula (Creatinine Clearance (mL/min) = (140 – age)(wt kg) / 72 x serum creatinine (mg/100 ml) [Cockcroft, 1976] at Screening.
10. Subject has uncontrolled hypertension as indicated by a resting systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg at Screening.
11. Subject has received an investigational agent within 4 weeks or 5 half lives whichever is longer prior to Day 1.
12. Subject has shown a hypersensitivity reaction to the active pharmaceutical ingredient or any of the capsule components, including Labrasol, butylated hydroxyanisole, and butylated hydroxytoluene.
13. Subject has any condition which, in the Investigator's opinion, makes the subject unsuitable for study participation.

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

4 TREATMENT(S)

4.1 Identification of Investigational Product

4.1.1 Enzalutamide

Enzalutamide has the chemical name 4-{3-[4-Cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide. It is a white to off-white solid that is insoluble in water and no salt forms are available at ~pH 2 to 10.

Enzalutamide capsules are white to off-white oblong capsules. The soft gelatin capsules are filled with a clear, yellowish solution which contains the two antioxidants, butylated hydroxyanisole, and butylated hydroxytoluene , and enzalutamide active ingredient (40 mg), all dissolved in the non-ionic surfactant, Labrasol® (Caprylocaproyl Polyoxylglycerides).

Enzalutamide should be stored in a secure location with limited access at 77°F (25°C), with excursions permitted to 59°F to 86°F (15°C to 30°C). Subjects will be instructed to store study drug at room temperature out of the reach of children.

4.1.2 Comparative Drug(s)

This section is not applicable as this is a single-arm study.

4.1.3 Seizure Therapy

Standard anticonvulsant measures, if indicated in the event of a seizure (NOTE: concomitant medication restrictions).

If the decision is made to continue a subject in the study after a first seizure, treatment including anti-seizure medication may be administered as recommended by the local neurologist and guided by the following restrictions.

- Enzalutamide has the potential to interact with some anti-seizure drugs.
- Acceptable drugs unlikely to cause interactions are
    - Levetiracetam
    - Gabapentin
    - Pregabalin
- Drugs which are acceptable but should be **administered with caution** include
    - Ethosuccimide
    - Lacosamide
    - Lamotrigine
    - Oxcarbazepine
    - Topiramate
    - Valproate
    - Zonisamide
- Benzodiazepines **should not be used** for maintenance therapy of seizure
- Other anti-seizure medications **not permitted in the study** include
    - Carbamazepine
    - Phenytoin
    - Phenobarbital
    - Primidone
    - Felbamate
    - Vigabatrin
    - Retigabine

4.2 Suspected Seizure Event Management

Each subject will be given a patient card with the following information; a list of signs and symptoms of a suspected seizure (Seizure Description Subject Information) and a Suspected Seizure Event Questionnaire list as well as instructions regarding what to do in the event of a suspected seizure for awareness.

The subject will contact the Investigator immediately (within 24 hours) after onset of a suspected seizure event and return to the site with best efforts in 3 days after event for evaluation by the local neurologist.

Investigator will:

- Instruct the subject to stop taking the enzalutamide study drug until after the clinical assessment has been completed by the neurologist. (Note: this could be a temporary stoppage, if the event turns out not to have been deemed a seizure, or is a 1st seizure with good benefit/risk ratio for continuing study drug.)
- Instruct the subject to complete the Suspected Seizure Event Questionnaire with input from any witness(es) to suspected events.
- Schedule a clinic visit to be evaluated by the local neurologist.

Evaluation by a local neurologist is required including electroencephalogram (EEG) and magnetic resonance imaging (MRI) procedures as soon as possible after a potential seizure event occurrence. A description of the events leading up to the seizure will be obtained from the individual and any witnesses.

The study site will interview the subject and any witnesses, if possible, regarding the event. The study site will complete a Suspected Seizure Event Questionnaire including a Cover Sheet which will be signed by the PI/Sub-Investigator and included as part of the package to the IAC. The site will review the Suspected Seizure Event Questionnaire completed by the subject, if available. The subject Suspected Seizure Event Questionnaire is a tool to capture information of the suspected event which the PI/Sub-Investigator will utilize for completion of their evaluation when available. The Questionnaire completed by the subject will not be collected.

Subjects will be treated as indicated by the local neurologist including acceptable anti-convulsants. Anticonvulsant substrates of CYP3A4, CYP2C9 or CYP2C19 with a narrow therapeutic index are **not** permitted (e.g., anticonvulsant medications including carbamazepine, phenytoin, phenobarbital, primidone, felbamate, vigabatrin, and retigabine).

Subjects may continue on enzalutamide at the discretion of Investigator while the evaluation for a first possible seizure is ongoing. The dose of enzalutamide may be continued while the subject is on treatment with anticonvulsant therapy. If a subject experiences a second confirmed seizure by IAC, the subject will be discontinued from the study.

All relevant information, including the completed seizure assessment questionnaire, the local neurologist's evaluation, and results of the MRI of the brain and EEG, will be submitted to the IAC for evaluation. Results of the assessment of the IAC will be provided to the Investigator and the subject will be allowed to continue in the study if the event is determined to be a first confirmed seizure. If the seizure is determined by the IAC to be a second confirmed seizure event in the study, the subject will be withdrawn from the study. If it is determined that the event did not meet criteria for a confirmed seizure, the subject can continue in the study if no other discontinuation criteria have been met.

4.3 Packaging and Labeling

Enzalutamide used in this study will be prepared, packaged, and labeled, and final release under the responsibility of qualified staff at Astellas US Technologies, Inc (AUST) or designee in accordance with AUST Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH GCP guidelines, and applicable local laws/regulations.

Enzalutamide capsules are packaged in a white, opaque, high-density polyethylene (HDPE) bottles. Each bottle will bear a label conforming to regulatory guidelines, Good Manufacturing Practice and local laws and regulations which identifies the contents as investigational drug.

Site pharmacist or medically qualified staff will dispense the study treatment to each subject in accordance with this protocol.

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.

4.4 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 and is only dispensed to study subjects in accordance with the protocol, and
- that any unused study drug is returned to the Sponsor.

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

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

- The site must return study drug to the Sponsor or designee at the end of the study or upon expiration unless permission to destroy the study drug at the site is granted by the Sponsor.

4.5 Blinding

This section is not applicable as this is an open-label study.

4.6 Assignment and Allocation

Assignment will be performed via Interactive Response Technology (IRT). IRT will be used for the management of enrollment, screening, subject tracking and clinical supplies. Specific procedures for assignment through the IRT are contained in the study procedures manual.

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Enzalutamide and Other Medication(s)

5.1.1 Dose/Dose Regimen and Administration Period

Subjects will be instructed to take 4 capsules (40 mg each) per day orally. Enzalutamide may be taken with or without food and should be taken as close to the same time each day as possible. The total duration of treatment is 4 months. At the end of the 4-month treatment period, subjects who are assessed as deriving benefit from enzalutamide treatment may continue in the extension period. Subjects in the extension period may continue to receive enzalutamide until they experience bone disease progression per PCWG2 guidelines or soft tissue disease progression per RECIST 1.1, they initiate treatment with another anticancer therapy, continued dosing would lead to undue risk to the subject in the opinion of the Investigator, they meet a discontinuation criterion or the Sponsor terminates the study. The total study drug treatment duration for the extended period will depend on individual clinical benefit to enzalutamide treatment.

Subjects who are continuing to receive clinical benefit from treatment with enzalutamide and have not met any discontinuation criteria may transition to an open label roll-over extension study upon approval of the study protocol at the institution they are receiving treatment at.

5.1.2 Increase or Reduction in Dose of Enzalutamide

Subjects who experience a Grade 3 or higher toxicity that is attributed to enzalutamide and cannot be ameliorated by the used of adequate medical intervention may interrupt treatment with enzalutamide for 1 week or until the toxicity grade improves to Grade 2 or lower severity. Subsequently, study drug dosing may be restarted at the original dose (160 mg/day) or a reduced dose (120 or 80 mg/day) in consultation with the Medical Monitor.

If the adverse event is considered not related to enzalutamide by the Investigator, enzalutamide may be resumed at the same dose.

If the adverse event is considered possibly or probably related to enzalutamide, enzalutamide may be resumed with medical monitor approval either at the same dose or at a reduced dose of 120 or 80 mg/day once daily.

If enzalutamide is co-administered with a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily. If co-administration of strong CYP2C8 inhibitor is discontinued, the enzalutamide dose should return to the dose used prior to initiation of the strong CYP2C8 inhibitor.

The Sponsor Medical Monitor may be contacted with any questions or concerns on managing dose.

5.1.3 Previous and Concomitant Treatment (Medication and Non-Medication Therapy)

Medication taken within four weeks prior to Screening visit will be collected.

All concomitant medications must be documented at each visit, at the time of discontinuation, and at the 30 day follow-up visit.

The following medications are prohibited during the course of the study:

- Therapies to treat prostate cancer including but not limited to:
  - Cytotoxic chemotherapy
  - Hormonal therapies (e.g., anti-androgens, abiraterone acetate, estrogens; testosterone, dehydroepiandrosterone [DHEA], etc.), 5-alpha reductase inhibitors, ketoconazole;
  - Anticonvulsant substrates of CYP3A4, CYP2C9 or CYP2C19 with a narrow therapeutic index (e.g., carbamazepine, phenytoin, phenobarbital, and primidone are not permitted in this study. Felbamate, vigabatrin, and retigabine are also not permitted for reasons of potential toxicity.
- Note: GnRH analogues (agonists or antagonists), bone-targeting agents, such as bisphosphonates and denosumab, and glucocorticoids are allowed. Palliative radiotherapy is also allowed (provided the subject does not meet discontinuation criteria).
- Any other investigational agent.

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) or inducers (e.g. rifampicin) are to be avoided. If subject must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide must be reduced to 80 mg once daily. If a co-administration of the strong inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.
- Enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Uridine 5'-diphospho-glucuronosyltransferase (UGT1A1) may also be induced. Medicinal products with a narrow therapeutic range that are substrates of CYP3A4, CYP2C9, CYP2C19, or UGT1A1 should be used with caution when administered concomitantly with enzalutamide and may require dose adjustment to maintain therapeutic plasma concentrations. Such substrates include, but are not limited to:

- Macrolide antibiotics (e.g. clarithromycin)
- Benzodiazepines (e.g. diazepam, midazolam, alprazolam, triazolam)
- Immune modulators (e.g. cyclosporine, tacrolimus)
- HIV antivirals (e.g. indinavir, ritonavir)
- Anti-epileptics (e.g. phenobarbital, phenytoin).
- Coumarins (e.g. warfarin)

- If enzalutamide is co-administered with warfarin (CYP2C9 substrate), additional INR monitoring should be conducted.
- Medicinal products with a narrow therapeutic range that are substrates for P-gp (e.g., digoxin, colchicine, dabigatran etexilate) or for the breast cancer resistant protein (BCRP) or the multidrug resistance-associated protein 2 (MRP2), should be used with caution when administered concomitantly with enzalutamide and may require dose adjustment to maintain optimal plasma concentrations.
- No other new systemic therapy or new radiotherapy for treatment (exception for spinal cord compression, pain management, etc) for prostate cancer is permitted while subject is on the study. Subjects with pre-existing non-target lesions (e.g., bone metastases) receiving palliative radiography for pain treatment before participation in the study are allowed to continue receiving radiotherapy during the study.

5.1.4 Treatment Compliance

Study subjects should be counseled on the need to meet 100% compliance with study drug. 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 at each monthly visit after Baseline. When study drug is administered at the research facility, it will be administered under the supervision of study personnel.

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

If compliance is 80%, the Investigator or designee is to counsel the subject and ensure steps are taken to improve compliance. Subjects who are less than 80% compliant with the dosage regimen for any two consecutive visit periods during the study should be withdrawn from the study.

Treatment compliance should be monitored closely and deviation in compliance should be reported to the Sponsor.

5.1.5 Criteria for Continuation of Treatment

At the end of the 4-month treatment visit, subjects who are assessed as deriving benefit from enzalutamide treatment may continue in the extension period. Subjects in the extension period will continue to receive enzalutamide until they experience bone disease progression per PCWG2 guidelines or soft tissue disease progression per RECIST 1.1, they initiate treatment with another anticancer therapy, continued dosing would lead to undue risk to the

subject in the opinion of the Investigator, they meet a discontinuation criterion or the Sponsor terminates the study.

When any subject who continues on treatment after his 12-month extension period, data collection will be limited to dosing information, concomitant medications and all AEs including serious adverse events (SAEs),

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

Demographic information is to be obtained at screening and will include date of birth or age as local regulations allow, ethnicity, race as described by the subject, height and weight. It is anticipated that the age range of subjects enrolled in this study would be similar to that of patients with mCRPC in general. In AFFIRM, the pivotal phase 3 study of enzalutamide the median age was 69 years (range 41-92).

5.2.2 Medical History

Medical history will include any significant conditions or diseases other than prostate cancer that occurred prior to informed consent. Subjects with a history of alcoholism are permitted to enroll in the study if eligibility criteria are met. Subjects with Alzheimer's disease are permitted to be enrolled into the study based on existing clinical diagnosis.

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

A complete medical history of the target disease will be recorded at screening. This includes documenting the subject's initial diagnosis of prostate cancer, Gleason score at time of diagnosis dates and type of primary therapy and other disease specific information as designated in the eCRF.

5.3 Efficacy | Pharmacodynamics | Pharmacokinetics Assessment

Assessments of efficacy, pharmacokinetics, and pharmacodynamics will not be performed for this protocol.

5.4 Safety Assessment

5.4.1 Vital Signs

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

5.4.2 Adverse Events

See Section 5.5 Adverse Events and Other Safety Aspects for information regarding adverse event collection and data handling.

Adverse events will be collected from time of study drug administration on Day 1 until 30 days after last dose of enzalutamide.

Serious adverse events (SAEs) including death will be collected from the time the subject signs the consent form until 30 days after last dose of enzalutamide.

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 liver function testing (LFT, e.g., AST, ALT, bilirubin, etc.) or is suspected to be due to hepatic dysfunction.

Subjects with AEs of hepatic origin accompanied by Liver Function Test (LFT) abnormalities should be carefully monitored.

5.4.3 Laboratory Assessments

Below is a table of the laboratory tests that will be performed during the conduct of the study. This study will utilize local laboratories. See Schedule of Assessments for study visit collection dates.

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

Routine laboratory assessments for hematology and chemistry will be collected and analyzed at the site laboratory. Laboratory assessments will be assessed at Screening and at each study visit as per the Schedule of Assessments.

The laboratory assessments performed at the Screening Visit do not need to be repeated on Day 1 if the Day 1 visit occurs within 72 hours of Screening.

Laboratory assessments must be obtained prior to study drug administration.

CHEMISTRY	HEMATOLOGY
Sodium (Na) Potassium (K) Chloride (Cl) Bicarbonate (HCO3) Blood Urea Nitrogen (BUN) Creatinine (Cr) Glucose Calcium (Ca) Phosphate (Pi) Magnesium (Mg) Albumin Total Protein Alkaline Phosphatase Lactate Dehydrogenase (LDH) Creatine Phosphokinase (CK) Liver Function Tests including: • Bilirubin Total (TBL) • Alanine Aminotransferase (ALT) • Aspartate Aminotransferase (AST)	White Blood Cell Count (WBC) WBC Differential Red Blood Cell Count (RBC) Hemoglobin (Hgb) Hematocrit (Hct) Mean Corpuscular Volume Platelet Count

5.4.4 Physical Examination

Standard, full physical examinations will be performed to assess weight, general appearance, head, eyes, ears, nose, throat, neck, cardiovascular, chest and lungs, abdomen, musculoskeletal, neurologic status (see Section 5.4.5 Neurological Examination), mental status, lymphatic, and genitourinary system. Any clinically significant abnormalities will be collected as medical history or adverse events. Weight and height will be recorded at the screening visit only. The physical examination performed at the screening visit does not need to be repeated on Day 1 if the Day 1 visit occurs within 72 hours of Screening visit.

5.4.5 Neurological Examination

At Screening, a thorough neurological history and examination will be performed by a local neurologist to obtain complete medical history relating to seizure risk, to confirm that a subject has met seizure risk entry criteria and to complete neurological baseline examination.

5.4.6 Seizure Evaluation by a Neurologist

If a suspected seizure event occurs, an evaluation by a local neurologist is required including electroencephalogram (EEG) and magnetic resonance imaging (MRI) procedures as soon as possible after a potential seizure event occurrence.

5.4.7 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed on all subjects at Screening, Week 13, End of Treatment (EOT), 30 days post treatment and Suspected Seizure visit, if applicable. Parameters that include heart rate, PR interval, RR interval, QRS interval, QT interval will be collected on the (e)CRF. Abnormalities and clinical significance as judged by the Investigator will be reported as well.

An ECG will be performed as per schedule of assessment. All ECGs will be performed prior to study drug administration. The subject should have rested in supine position (or semi-recumbent, if supine is not tolerated) for 5-10 minutes.

5.4.8 Performance Status

The ECOG scale [Oken et al, 1982] will be used to assess performance status at Screening.

Table 2 ECOG Performance Status

Grade	Description
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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events (AEs)

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.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one 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.

Some countries may have additional local requirements for events that are required to be reported as AEs or in an expedited manner similar to an 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 eCRF accordingly.

5.5.2 Definition of Serious Adverse Events (SAEs)

An adverse event 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 adverse event 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 adverse event that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events

For the purpose of this study, all potential seizures will be reported as SAEs. Seizures due to enzalutamide overdose will be reported similar to all other seizure 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 one 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, background therapy) that may require expedited reporting and/or safety evaluation include, but are not limited to:

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

All of the events of interest noted above should be recorded on the (e)CRF. Any situation involving these events of interest that also meets the criteria for an SAE should be recorded on the AE page of the (e)CRF and marked 'serious' on the SAE worksheet.

The Sponsor has a list of events that they classify as "always serious" events. If an adverse event 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

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

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

5.5.4 Criteria for Defining the Severity of an Adverse Event

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

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

5.5.5 Reporting of Serious Adverse Events (SAEs)

In the case of a serious adverse event (SAE), the Investigator must contact the Sponsor by telephone or fax 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 by fax immediately (within 24 hours of awareness). If the faxing of an SAE Worksheet is not possible or is not possible within 24 hours, the local drug safety contact should be informed by phone.

For contact details, see Section II Contact Details of Key Sponsor's Personnel. Please fax the SAE Worksheet to:

Astellas Pharma Global Development, Inc. – United States
Product Safety & Pharmacovigilance, Fax number 1- (847) 317-1241;
Email: safety-us@us.astellas.com

If there are any questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Monitor/Expert 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 (e)CRF.

The following minimum information is required:

- ISN/Study number,
- Subject number, sex and age,
- The date of report,
- A description of the SAE (event, seriousness of the event), and

- Causal relationship to the study drug.

The Sponsor or Sponsor's designee will submit expedited safety reports (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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) within timelines set by regional regulations (i.e. EU, (e)CTD, FDA). Documentation of the submission to and receipt by the IRB/IEC of expedited safety reports should be retained by the site.

The Sponsor/delegated CRO will notify all Investigators responsible for ongoing clinical studies with the study drug of all SAEs which require submission per local requirements IRB/IEC / head of the study site.

The heads of the study sites/Investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor.

The Investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor.

You may contact the Sponsor's Medical Monitor/Expert for any other problem related to the safety, welfare, or rights of the subject.

For Suspected Unexpected Serious Adverse Reactions (SUSAR) from this trial, a CIOMS-I report will be submitted to the IRB/IEC where required. SUSAR will be submitted to the authorities by means of a MedWatch report (FDA) or an E2B report (Eudravigilance).

5.5.6 Follow-up of Adverse Events

Adverse event collection will begin at the time of the first dose of study drug and continue through approximately 30 days post last dose or immediately prior to start of another antineoplastic therapy. All adverse events reported during this safety reporting period are to be followed at appropriate intervals until resolution or until judged to be no longer clinically significant, or until the event becomes chronic to the extent that the event can be fully characterized or until new antineoplastic treatment is initiated.

If during AE follow-up, the adverse event progresses to an ″SAE″, or if a subject experiences a new SAE, the Investigator must immediately report the information to the Sponsor.

Please refer to Appendix 12.2 Liver Safety Monitoring and Assessment for detailed instructions on Drug Induced Liver Injury (DILI).

5.5.7 Monitoring of Common Serious Adverse Events

Common serious adverse events 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 your reference. The list does NOT change your reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed above. The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of “common serious adverse events” as specified in Appendix 12.3 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 during the conduct of a clinical trial (from first dose through the safety follow-up period approximately 30 days after discontinuation of dosing), a male subject makes his partner pregnant, the subject should report the pregnancy to the Investigator. The Investigator will report the pregnancy to the Sponsor in the same manner as 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.

The Investigator should report the outcome of the pregnancy (independent of outcome, e.g., full term delivery, pre-term delivery, spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried fetus), in accordance with the same reporting procedure as for SAEs. The date of outcome of the pregnancy, gestational age, date of birth and neonatal data, etc., should be included in this information. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below.

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

5.5.9 Emergency Procedures and Management of Overdose

There is no antidote for enzalutamide. In the event of an overdose, stop treatment with enzalutamide and initiate general supportive measures based on the clinical presentation of the patient. Subjects may be at increased risk of seizure following an overdose.

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 including the change in the most common serious adverse events

stated in Section 5.5.7. Investigators should inform the IRB/IEC of such information when needed.

5.6 Test Drug Concentration

Not applicable for this study.

5.7 Other Measurements, Assessments or Methods

5.7.1 Blood Sample for Future PGx Analysis (Retrospective PGx Analysis)

A PGx research may be conducted in the future to analyze or determine genes of relevance to clinical response, pharmacokinetics, and toxicity/safety issues. Any time during the Screening Period, and after the patient has signed the study PGx informed consent form (see schedule of assessments), a 5 mL sample of whole blood for possible retrospective PGx analysis will be collected using a vacutainer tube containing EDTA. After collection, gently invert the blood sample 8 to 10 times. The blood collection tube may either be stored upright at 4°C for up to 5 days prior to shipment or stored frozen at -20°C or below at the site for extended storage. Samples will be shipped to a Sponsor designated banking CRO.

Labels should uniquely identify each sample and contain at least:

- Protocol number (9785-CL-0403),
- Subject number, and
- Purpose and biological matrix (i.e., “biobanking”, “whole blood”).

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

See Appendix 12.4. Retrospective PGx Sub-study for further details on the banking procedures.

5.8 Total Amount of Blood

The total amount of blood collected for each subjects will vary depending on how long the subjects stays on the study. If a subject is found to have laboratory abnormalities or adverse events, additional blood may be drawn for evaluation and/or monitoring. Additional diagnostic blood for routine work may also be drawn.

In addition, the total amount of blood collected for each subject for the optional pharmaco-genomics (PGx) sample is approximately 4-6 mL.

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.

Subjects who are continuing to receive clinical benefit from treatment with enzalutamide and have not met any discontinuation criteria may transition to an open label extension study upon approval of the study protocol at the institution they are receiving treatment at. 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 adverse event 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.

The following safety/compliance events will result in the removal of subjects from enzalutamide therapy and from the study if:

- Any adverse event that is intolerable to the subject and that cannot be ameliorated by the use of adequate medical intervention, or that in the opinion of the Investigator would lead to undue risk to the subject if dosing continued;
- Any first confirmed seizure requiring treatment with maintenance anticonvulsant therapy if the only anticonvulsant(s) the patient can tolerate is carbamazepine, phenytoin, phenobarbital, primidone, felbamate, vigabatrin, or retigabine.
- Any second seizure confirmed by independent adjudication committee;
- Inability to maintain the absolute neutrophil count above 500/µL (Grade 4) or 500-1000/µL (Grade 3) with evidence of infection;
- Inability to maintain the platelet count above 25,000/µL (Grade 4) or 25,000-50,000/ µL (Grade 3) with spontaneous bleeding;
- Subject who has unequivocal evidence of disease progression (upon bone disease progression per PCWG2 guidelines or soft tissue disease progression per RECIST 1.1) or is no longer deriving clinical benefit;
- Subject who is, in the opinion of the Investigator or the Medical Monitor, grossly non-compliant with the protocol's requirements.

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

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

6.2 Discontinuation of the Site

If an Investigator intends to discontinue participation in the study, the Investigator must immediately inform the Sponsor.

6.3 Discontinuation of the Study

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

7 STATISTICAL METHODOLOGY

The statistical analysis will be coordinated by the responsible biostatistician of APGD. A Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specification for tables, listings, and figures to be produced. The SAP will be finalized before the database soft lock at the latest. Any changes from the analyses planned in SAP will be justified in the Clinical Study Report (CSR).

Prior to database lock, a final review of data and Table Listing Figures (TLFs) 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

Approximately four hundred (400) subjects will be enrolled to target approximately 350 evaluable subjects, assuming a drop-out rate of approximately 13% for this population and based on the recommendation from the FDA, respectively. Assuming the true incidence of seizure in the first 4 months as 0.93%, based on the incidence rate of 2.8 per 100 patient years, which is obtained from the previous studies and the sample size of 350, the chance of observing 5 or less subjects with seizure events is 88.9%. Given 5 out of 350 subjects, i.e., point estimate of 1.43%, the upper limit 95% exact confidence interval will be 3.31% and the width of the exact confidence interval will be 2.84%.

7.2 Analysis Set

7.2.1 Safety Analysis Set (SAF)

For the statistical summary of the safety data, the safety analysis set (SAF) will be used. The SAF consists of all subjects who took at least one dose of study medication, and will be used for safety analyses. 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.

7.2.2 Seizure Risk Evaluation Set (SRES)

For the statistical summary and analysis of seizure events, seizure risk evaluation set (SRES) will be used by including all evaluable subjects. An evaluable subject is defined as a subject with a confirmed seizure during the 4-month treatment period of the study or who completed at least 3 months (75%) of the planned treatment.

7.3 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized for the SAF. 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

Efficacy data will be collected at baseline and at the time of seizure event for this study. No statistical analysis will be conducted. Instead, disease assessments including clinical, radiographic and/or PSA assessments collected will be listed.

7.4.1 Analysis of Primary Endpoint

7.4.1.1 Primary Analysis

Primary endpoint, the proportion of evaluable subjects with at least one confirmed seizure as adjudicated by the IAC during the 4-month treatment duration will be analyzed estimated using point estimate and its 95% exact confidence interval using all SRES.

In case the drop-out rate is higher than expected, appropriate method such as Kaplan-Meier estimations [Kaplan and Meier, 1958; Greenwood, 1926] may be considered to efficiently estimate the proportion of seizure events with accounting for the censored observations in the SAF.

7.4.1.2 Secondary Analysis

The same analysis of the primary endpoint as described in 7.4.1.1 will be conducted for a cumulative proportion to include all seizure events, including those occurring beyond the 4 month-treatment period using all SRES. Incidence of seizure events per patient-time exposure will be summarized.

7.4.1.3 Subgroup Analysis

In case subgroups which may have association with the risk of seizure are identified during the study, the incidence of seizure events will be summarized using a proportion estimate and its 95% exact confidence interval for the subgroups of the SRES.

7.5 Analysis of Safety

7.5.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (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 will also be summarized. All AEs will be listed.

7.5.2 Laboratory Assessments

For quantitative laboratory measurements descriptive statistics will be used to summarize results and change from baseline by time point. Using the definitions provided in the NCI CTCAE Version 4.03, lab values will be classified as Grade 1 through 5, where possible. Shifts from baseline will be tabulated regarding either normal ranges or CTC CTCAE grade. Laboratory data will be displayed in listings and summary tables.

7.5.3 Vital Signs

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

7.5.4 Physical Examination Including Neurological Status

Physical examination including neurological status will be summarized.

7.5.5 ECGs

The 12-lead ECG results will be summarized.

7.6 Analysis of Pharmacokinetics

No pharmacokinetic analysis is planned.

7.7 Analysis of Pharmacodynamics

No pharmacodynamics analysis is planned.

7.8 Protocol Deviations and Other Analyses

Protocol deviations as defined in Section 8.1.6 Protocol Deviations will be listed by site and subject.

The protocol deviation criteria will be uniquely identified in the 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 (and Early Discontinuation of Subjects Subgroup)

No formal interim analysis is planned for a specific timepoint.

The DSMB will examine safety data and be informed on seizure events as expediently as possible. Statistical boundaries for continuously monitoring of the seizure event will be provided in the DSMB charter as a guidance for early stopping criteria. The DSMB will use them to appropriately recommend either stop the enrollment of specific risk factor group(s)

identified during the DSMB review period or in extreme circumstance DSMB may ask sponsor to stop the study.

The study design considers early stopping criteria that can be applied to a study as a whole or a specific risk factor group, if any, based on the statistical boundary calculated from Maximized Sequential Probability Ratio Test [Kulldorff, 2011]. Statistical boundary will be provided in the DSMB charter. Evaluation of the seizure risk is performed by DSMB for the study as a whole and for the risk factor group at the same time using the same stopping boundary based on false stopping probability of 0.1. Recommendation will be made by DSMB to either stop the study or stop further enrollment of a specific risk factor group.

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

As a general principle, no imputation of missing data will be done. Exceptions are the start and stop dates of AEs and concomitant medication. The imputed dates will be used to determine whether an AE is/is not treatment emergent. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

See the SAP for details of the definitions for windows to be used for analyses by visit.

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 the timeframe defined for the study 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.

Laboratory tests are performed at local laboratory.

For Screen failures the demographic data, reason for failing, informed consent, inclusion and exclusion criteria will be collected in the eCRF.

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. 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, sex, race, ethnicity, height and body weight)
- Inclusion and exclusion criteria details
- Participation in study and original signed and dated informed consent forms
- Visit dates
- Medical history and physical examination details
- Key efficacy and safety data, if applicable (as specified in the protocol)
- Adverse events and concomitant medication
- Results of relevant examinations (e.g., ECG charts, X-ray films etc.)
- Laboratory printouts (if applicable)
- Dispensing and return of study drug details
- Reason for premature discontinuation (if applicable)
- Randomization number (if applicable)

8.1.3 Clinical Study Monitoring

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

8.1.4 Direct Access to Source Data/Documents

The Investigator and the study site must accept monitoring and auditing by the Sponsor or delegated CRO 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 Global Data Science department of the Sponsor in accordance with the standard operating procedures (SOPs) for data management. All study specific processes and definitions will be documented by Data Management. (e)CRF completion will be described in the (e)CRF instructions. Coding of medical terms and medications will be performed using MedDRA and World Health Organization (WHO) 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 (TMF).

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

8.1.7 End of Trial in All Participating Countries

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

8.2 Ethics and Protection of Subject Confidentiality

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

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent 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 serious adverse events 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 one 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 within one year after last subject out (LSO) or termination of the study.

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 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 including information regarding treatment options (abiraterone, chemotherapy, etc) and signed and dated by the subject or his guardian or legal representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed informed consent form 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.

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 re-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 informed consent form. A copy of the signed informed consent form 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 re-consent 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.

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 (PHI) obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information (i.e. HIPAA).

8.3 Administrative Matters

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

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

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

8.3.2 Documents and Records Related to the Clinical Study

The 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 and SAE Report Worksheet
- 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 CRF
- Current Curricula Vitae of all investigators
- List of sub-investigators and collaborators
- IRB approval of the protocol, protocol amendments (if applicable) including a membership list with names and qualification (COPY)
- Instruction and decision of the head of the study site
- Study contract
- Laboratory normal reference ranges (if applicable, signed and dated by the responsible laboratory employee)

At the end of the study, the sponsor is responsible for the collection of:

- Unused study documentation,
- Unused study drug

The Investigator will archive all study data (e.g., Subject Identification Code List, source data, eCRFs, and Investigator's File) and relevant correspondence. These documents are to

be kept on file for the appropriate term determined by local regulation (for US sites, two 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 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 on the eCRFs supplied for each subject.

The Investigator and sponsor will mutually agree upon the storage format for the retention of electronic data.

8.3.3 Protocol Amendment and/or Revision

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

Amendments to this protocol must be signed by the Sponsor and the Investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented which affects 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.

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, case report forms, and source documents. Direct access to these documents will be required by the auditors.

10 STUDY ORGANIZATION

10.1 Data and Safety Monitoring Board (DSMB) | Independent Adjudication Committee (IAC)

A DSMB will be established for this study and remain active for the study duration. The DSMB will examine safety data and be informed of seizure events as expediently as possible.

The role and responsibilities of the DSMB will be described in the DSMB charter which will be in place for the start of the study. Details of statistical boundaries for monitoring of the seizure event will be provided in the DSMB charter.

An IAC will be established to assess all suspected seizure events occurring during the study. The committee will consist of independent members of appropriate expertise who are not directly involved in the conduct of the clinical study. Suspected seizure adverse events and related information of the cases will be sent to the committee for assessment. A separate charter will describe the classification of those events to be adjudicated and the specification of the event-related documents, listings, data flow, method(s) for data collection, and any applicable data transfers.

11 REFERENCES

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Enzalutamide Investigator's Brochure

12 APPENDICES

12.1 List of Drugs that May Lower Seizure Threshold

Category	Drug
Antiasthmatics	Aminophylline, theophylline
Antibiotics	Isoniazid, lindane, metronidazole, nalidixic acid, penicillins, and certain cephalosporins
Antidepressants	Tricyclics, serotonin-specific agents, bupropion, mirtazepine
General anesthetics	enfluraneketamine
Hormones	Insulin, estrogen
Immunosuppressants	Chlorambucil, cyclosporine
Local anesthetics	Lidocaine, bupivicaine, procaine
Narcotics	Fentanyl, meperidine, pentazocine, propoxyphene
Psychostimulants	Amphetamines, cocaine, methylphenidate, phenylpropanolamine
Neuroleptics	Anti-psychotics including but not limited to clozapine, phenothiazines, butyrophenones; also the anti-emetic prochlorperazine.
Other	Anticholinergics, anticholinesterases, antihistamines, baclofen, heavy metals, hyperbaric oxygen, lithium, mefenamic acid, oral hypoglycemic, oxytocin

Source include from: http://professionals.epilepsy.com/page/table_seniors_drugs html

12.2 Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy who reveals an increase of serum aminotransferases (AT) to > 3 × ULN (to > 5 × ULN in subjects with liver metastases), or bilirubin > 2 × ULN, should undergo detailed testing for liver enzymes (including at least ALT, AST, ALP, and TBL). Testing should be repeated within 48-72 hours of notification of the test results. For studies in which a central laboratory is used, alerts will be generated by the central lab regarding moderate and 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 and severe where ULN:

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

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

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks (in the absence of liver metastases)
- ALT or AST > 3 × ULN and INR > 1.5 (If INR testing is applicable/evaluated).
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

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

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The site should complete the Liver Abnormality Case Report Form (LA-eCRF) that has been developed globally and can be activated for the study. Subjects with confirmed abnormal liver function testing 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 a Serious

Adverse Event (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 'adverse events' on the AE page of (e)CRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Non-alcoholic steatohepatitis (NASH) is seen in obese hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels. The Investigator should ensure that the medical history form captures any illness that pre-dates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including non-prescription medication, complementary and alternative medications), alcohol use, recreational drug use, and special diets. Medications, including dose, should be entered on the concomitant medication page of the (e)CRF. Information on alcohol, other substance use, and diet should be entered on the LA-eCRF 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-eCRF or an appropriate document.

Study Discontinuation

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

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

In addition, if close monitoring for a 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 two "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 3 times the upper limit of normal ("2 x ULN elevations are too common in treated and untreated patients to be discriminating"). 2. Cases of increased bilirubin (at least 2 x ULN) with concurrent transaminase elevations at least 3 x ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's syndrome. [Temple R. Hy's law: predicting serious hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006 Apr;15(4):241-3.]

Reference

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

12.3 Common Serious Adverse Events

The following is a list of serious adverse events that the Sponsor considers to be common for the study population defined in this protocol and should be reported by the Investigator as described in Section 5.5.5 Reporting of Serious Adverse Events (SAE).

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 indicate they occur more frequently with study drug, an expedited IND safety report may be submitted to the FDA.

- Anemia
- Anorexia
- Asthenia / Fatigue
- Back pain
- Bone pain
- Catheter related infection
- Dyspnea
- Haematuria
- 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 PGx Sub-Study

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 (GWAS), the relationship between gene profiles and a drug's kinetics, efficacy or toxicity may be better understood. As many diseases may be influenced by one 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 sub-study. As part of this sub-study, 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 sub-study will provide one 4-6 ml tube of whole blood per Astellas' instructions. Each sample will be identified by the unique subject number (first code). Samples will be shipped frozen to a designated banking CRO either directly from site or via a central laboratory as directed by Astellas.

BANKING CRO STORAGE AND SAMPLE CODING

Once received at the banking CRO, the samples will be assigned a unique sample code (second code) and stored frozen. A table linking the subject number (first code) with the newly-assigned sample code (second code) will be kept by the banking CRO.

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. Prior to initiating any analysis on the banked samples, the Astellas ethical committee (AREC) must approve the analysis plan.

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 Planned Countries

Argentina, Australia, Belgium, Brazil, Canada, Chile, Czech Republic, Finland, France, Germany, Greece, Hong Kong, Hungary, Israel, Italy, Mexico, New Zealand, Russia, Singapore, South Korea, Spain, Sweden, Taiwan, United Kingdom, United States

12.6 Study Milestones

Following are the planned study milestone dates:

Start of Data Collection	September 2013
End of Data Collection or Date of Early Termination, if applicable	June 2018
Study Progress Report(s)	Progress reports will be submitted as agreed with relevant national competent authorities or in any periodic safety reports and RMP updates, where applicable
Interim Report(s) of Study Results, where applicable	No formal interim analysis is planned for the study
Final Report of Study Results	March 2019
Date of Protocol Approval by IRB/EC	US (August 2013)

13 ATTACHMENT 1: NON-SUBSTANTIAL AMENDMENT 3

I The purpose of this amendment is:

Non-Substantial Changes
1. **Update contact information**
DESCRIPTION OF CHANGE
Update contact information to reflect the current responsible personnel.
RATIONALE
Astellas Sponsor contact information has been updated to identify current and additional study team.
2. **Update to study design, dose regimen and discontinuation**
DESCRIPTION OF CHANGE
Update the continuation and duration of subjects who receive enzalutamide to roll-over to a separate open-label extension study.
RATIONALE
The sponsor may decide to potentially roll-over subjects who receive enzalutamide and clinical benefit the treatment, and not have met any discontinuation criteria, to continue into a separate Astellas sponsored open-label extension study.
3. **Update to criteria for continuation of treatment**
DESCRIPTION OF CHANGE
Addition of concomitant medications to criteria for continuation of treatment when subjects continued in the extension period, and revision of text.
RATIONALE
Concomitant medications were omitted from the previous protocol when subjects continued in the extension period.

II. Amendment Summary of Changes:

II Contact Details of Key Sponsor's Personnel
DELETED:
~~Additional Medical Contact (Neurology)~~ PPD ~~, Global Medical CNS Science~~ PPD PPD ~~, Global Clinical Science~~ PPD PPD ~~, Global Clinical Science~~ PPD PPD ~~, Global Clinical Science~~ PPD
ADDED:
PPD **, Global Clinical Science** PPD PPD **, Global Clinical Science** PPD

IV Synopsis *Study Design Overview*
WAS:
Subjects who do not wish to continue in the extension period or who meet a discontinuation criterion will be discontinued from enzalutamide therapy and complete a 30-day follow-up visit from the last dose of enzalutamide.
IS AMENDED TO:
Subjects ~~who do not wish to continue in the extension period or~~ who meet a discontinuation criterion will be discontinued from enzalutamide therapy and complete a 30-day follow-up visit from the last dose of enzalutamide

IV Synopsis, 2 Study Objectives, Design, and Endpoints, 5. Treatments and Evaluation, 6 Discontinuation *Study Design Overview, Section 2.2.1 Study Design, Section 5.1.1Dose/Dose regimen and Administration, Section 6.1 Discontinuation of Individual Subject(s)*
ADDED:
Subjects who are continuing to receive clinical benefit from treatment with enzalutamide and have not met any discontinuation criteria may transition to an open label roll-over extension study upon approval of the study protocol at the institution where they are receiving treatment.

IV Synopsis *Duration of Treatment*
ADDED :
Subjects may be asked to complete their extension period participation in another Astellas sponsored study upon activation of the roll-over extension study at the institution.

IV Synopsis *Table 1: Schedule of assessments, footnote j and k*
WAS:
j. Extension period will begin for subjects who are assessed as deriving benefit from enzalutamide treatment after completion of the 4-month treatment. For any subject who continues on treatment after his 12-month extension period, data collection will be limited to dosing information, and all AEs including SAEs. k. For only subjects continuing in the extension period.
IS AMENDED TO:
j. Extension period will begin for subjects who are assessed as deriving benefit from enzalutamide treatment after completion of the 4-month treatment. For any subject who continues on treatment after his 12-month extension period, data collection will be limited to dosing information, **concomitant medication**, and all AEs including SAEs**. Subjects continuing into the extension period may be asked to complete their extension period participation in another Astellas sponsored study upon activation of the roll-over extension study at the institution. A Follow-up visit will not be required if subject move into the roll-over extension study.** k. For only subjects continuing in the extension period **who do not continue into the roll-over extension study at the institution.**

5.1 Treatments and Evaluation *Section 5.1.5, Criteria for Continuation of Treatment*
WAS:

When any subject who continues on treatment after his 12-month extension period, data collection will be limited to dosing information and all AEs including SAEs.
IS AMENDED TO:
When any subject who continues on treatment after his 12-month extension period, data collection will be limited to dosing information**, concomitant medications** and all AEs including SAEs.

III. Non-Substantial Amendment Rationale:

Rationale for Non-Substantial Designation
All revisions made to the protocol are administrative in nature and do not impact the safety or scientific value of the clinical study.

14 SPONSOR'S SIGNATURES