Abbreviated Title: Enzalutamide Formulation PK
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Title: A Bioequivalence Study to Compare Capsule and Liquid Formulations of Enzalutamide After Single Dose Administration Under Fasting Conditions in Prostate Cancer

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Commercial Agent: Enzalutamide

PRÉCIS

Background:

- Enzalutamide is currently approved for the treatment of patients with mCRPC
- The marketed (reference) formulation of enzalutamide is a liquid-filled, soft gelatin capsule containing 40 mg enzalutamide dissolved in Labrasol; four such capsules are required to deliver a 160 mg dose
- The four-capsule regimen is inconvenient because of the number of capsules that must be taken, particularly in light of the fact that cancer patients usually have to take multiple drugs.
- Additionally, some patients may not be able to swallow pills; therefore, alternate methods of oral administration are necessary

Objectives:

- To evaluate the bioequivalence, safety, and tolerability of two oral formulations of enzalutamide following a single 160 mg dose in male subjects with prostate cancer under fasting conditions.

Eligibility:

- Male subjects with prostate cancer

Design:

- Comparative, randomized, open-label, single-dose, 2-way crossover bioavailability, safety and tolerability study
- Subjects will be randomized in Period 1 to one of two sequences: AB or BA. Following a minimum 42-day washout period, subjects will be crossed over in Period 2 to receive the treatment that they did not receive in Period 1.
- Treatment A will be the standard capsule (reference) formulation; Treatment B will be the liquid formulation (test product)
- Blood samples will be collected for pharmacokinetic analysis

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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- To evaluate the bioequivalence of two oral formulations of enzalutamide following a single 160 mg dose in male subjects with prostate cancer

1.1.2 Secondary Objective

- To evaluate the safety and tolerability of two oral formulations of enzalutamide following a single 160 mg dose in male subjects with prostate cancer.

1.2 BACKGROUND AND RATIONALE

It is expected that 26,120 men will die from prostate cancer in the US in 2016 [1]. While some men are definitively treated for localized disease, many men will ultimately develop castrate resistant prostate cancer (CRPC) and succumb to the disease. Treatment options typically involve radical prostatectomy (RP) or radiation therapy in combination with androgen deprivation therapy. Following RP upwards of 50% of patients with high-risk disease will experience a biochemical recurrence at 5 years [2], and approximately 30% will die of their disease in 10-15 years [3].

1.2.1 Enzalutamide Background

Oral enzalutamide (160mg once daily) is currently approved in more than 40 countries for the treatment of metastatic castration-resistant prostate cancer (mCRPC). Enzalutamide acts on several steps of the androgen receptor (AR) pathway by inhibiting binding of androgen to the ligand binding domain of the AR, translocation of AR to the nucleus, and interaction of AR with DNA [4]. The efficacy and safety of enzalutamide was assessed in two randomized, placebo-controlled, multicenter phase III clinical trials (AFFIRM and PREVAIL) [5, 6].

Enzalutamide is a Biopharmaceutics Classification System (BCS) class 2 drug substance (low solubility, high permeability). It has been previously shown that lipid-based formulations work well with this drug class. The commercial product is a liquid-filled, soft gelatin capsule containing 40 mg enzalutamide dissolved in caprylocaproyl polyoxylglycerides (Labrasol).

1.2.2 Pharmacokinetic Studies

Multiple clinical pharmacokinetic studies of enzalutamide have been conducted [7]. Enzalutamide has a half-life of 5.8 days, achieves steady state by day 28, accumulates 8.3-fold with once-daily dosing, shows approximate dose proportionality from 30–360 mg/day, and has <30 % intersubject variability. It is primarily eliminated by hepatic metabolism, while renal excretion is an insignificant elimination pathway for enzalutamide and its active metabolite, N – desmethyl enzalutamide. Exposure to enzalutamide active moieties is not affected by food or baseline mild or moderate hepatic impairment. Enzalutamide has predictable pharmacokinetics, with low intersubject variability. Similar efficacy was observed in patients across the concentration/exposure range associated with a fixed oral dose of enzalutamide 160 mg/day.

Study NCT01911715 was a phase I, open-label, one-period, single-dose mass balance and biotransformation study in six healthy male subjects [7]. After a single oral dose of enzalutamide 160 mg (4 x 40 mg capsules), at least 84.2% of the drug was absorbed. The average C_{max}, t_{max}, AUC_{inf}, and $t_{1/2}$ of enzalutamide were 4.5 ug/mL, 1.8 h, 237 ug*h/mL, and 2.9 days, respectively.

A phase I, open-label, randomized, single-dose, parallel design, food-effect study was performed in 60 healthy men (n=30 in fasted and fed arms) to determine the effect of a high-fat meal on the pharmacokinetics of enzalutamide [7]. The average C_{max} and T_{max} for the fasted and fed arms were 5.3 and 3.7 ug/mL and 1 and 2h post-dose, respectively. The average AUC_{inf} for the fasted and fed arms were 292 and 285 ug*h/mL, respectively. In all, the data suggest that consumption of a high-fat meal slightly slows the rate of absorption but does not lower exposure of enzalutamide.

Gibbons et al. conducted two phase I drug interaction studies: one investigating the effects of coadministered drugs on the pharmacokinetics of enzalutamide, and one investigating the effects of enzalutamide on the pharmacokinetics of coadministered drugs [8]. Study NCT01913379, which used a parallel-treatment design (n=41), studied the effects of a strong CYP2C8 inhibitor (p.o. gemfibrozil 600 mg twice daily) and a strong CYP3A4 inhibitor (p.o. itraconazole 200 mg once daily) on the pharmacokinetics of enzalutamide after a single dose of enzalutamide (160 mg). Coadministration of gemfirozil and itraconazole increased the AUC_{inf} of enzalutamide by 2.2- and 1.3-fold, respectively. Study NCT01911728, which used a single-sequence cross-over design (n=14), studied the effects of enzalutamide (160 mg/day) on the pharmacokinetics of a single oral dose of sensitive substrates for CYP2C8 (picoglitazine 30 mg), CYP2C9 (warfarin 10 mg), CYP2C19 (omeprazole 20 mg), or CYP3A4 (midazolam 2 mg). The AUC_{inf} of warfarin, omeprazole, and midazolam were decreased by 56, 70, and 86%, respectively, after coadministration of enzalutamide, suggesting that enzalutamide is a moderate inducer of CYP2C9 and CYP2C19 and a strong inducer of CYP3A4.

A randomized, two-period crossover pilot bioequivalence and food effect study was carried out in 60 healthy male subjects to compare two enzalutamide formulations [9]. The reference formulation, which had previously been used in human clinical trials, was a liquid-filled soft gelatin capsule containing 40 mg enzalutamide dissolved in Laprasol. Four capsules were necessary to deliver 160 mg enzalutamide. The test formulation was a tablet composed of 160 mg enzalutamide in a 60%A:hydroxypropyl methylcellulose acetate succinate (HPMCAS)-M spray dried dispersion. While cohorts A and B (n=15, each) were fasted, cohorts C and D (n=15, each) were fed. Cohorts A and C were given a single dose of 160 mg enzalutamide as a tablet. Cohorts B and D were given a single dose of 160 mg enzalutamide as 4x40 mg liquid-filled capsules. After a 42-day washout, cohorts A and B, C and D were crossed over. The average AUC_{day1-7} for the tablet and capsule formulations in fasted subjects was 177 and 185 ug*h/mL, respectively. The average $AUC_{day}1-7$ for the tablet and capsule formulations was 191 and 187 ug*h/mL, respectively. In all, the data suggest that the bioequivalence of the formulations was comparable.

1.2.3 Rationale for an Oral Formulation of Enzalutamide

The reference formulation is a liquid-filled, soft gelatin capsule containing 40 mg enzalutamide dissolved in Labrasol; four such capsules are required to deliver a 160 mg dose. The liquid-filled capsule formulation had previously been used in clinical studies in castration-resistant prostate cancer and is currently the marketed formulation. The four-capsule regimen is inconvenient because of the number of capsules that must be taken per dose, particularly in light of the fact that cancer patients often have to take multiple drugs. In addition, some patients may have difficulty with swallowing. Therefore, alternate methods of oral administration are necessary.

1.2.4 Summary

This is a single-dose randomized, open-label, 2-way crossover pilot bioequivalence study to compare two oral formulations of enzalutamide. The reference formulation is a liquid-filled, soft gelatin capsule containing 40 mg enzalutamide dissolved in Labrasol; four such capsules are required to deliver a 160 mg dose. The test formulation is a liquid enzalutamide formulation prepared by extracting the liquid from the gelatin capsule. Patients will be dosed under fasting conditions, which involve nothing to eat or drink 2 hours prior to dosing and 2 hours after dosing is complete.. The pharmacokinetics of each method of administration will be studied to see if a liquid formulation of enzalutamide is a viable alternate to dosing as a capsule.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have histologically or cytologically confirmed prostate cancer . Note: If histopathological documentation is unavailable, a clinical course consistent with prostate cancer is acceptable.

2.1.1.2 ECOG performance status 0 to 2 (see APPENDIX A)

2.1.1.3 Patients must have adequate organ and marrow function as defined below:

– Hemoglobin	≥ 9 g/dL
– leukocytes	≥ 3,000/mcL
– absolute neutrophil count	≥ 1,500/mcL
– platelets	≥ 150,000/mcL
– total bilirubin	within normal institutional limits
– AST(SGOT)/ALT(SGPT)	≤3 X institutional upper limit of normal
– creatinine	within normal institutional limits
	OR
– creatinine clearance	≥ 30 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal (calculated via Cockcroft-Gault equation)

2.1.1.4 Patients must not have other concurrent malignancies (within the past 2 years with the exception of non-melanoma skin cancer and Rai Stage 0 chronic lymphocytic leukemia), in situ carcinoma of any site, or life threatening illnesses, including untreated

infection (must be at least 1 week off intravenous antibiotic therapy before beginning enzalutamide).

2.1.1.5 Ability of subject to understand and the willingness to sign a written informed consent document.

2.1.1.6 Willingness to travel to NIH for follow-up visits.

2.1.1.7 Men age ≥ 18 years of age. Children are excluded because prostate cancer is not common in pediatric populations. Women are not eligible because this disease occurs only in men

2.1.1.8 The effects of enzalutamide on the developing human fetus are unknown. For this reason men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) throughout the course of the study and for 3 months after the last dose. Should a woman become pregnant or suspect she is pregnant while her partner is participating in this study, she should inform her treating physician immediately.

2.1.2 Exclusion Criteria

2.1.2.1 Patients who are receiving any other investigational agents (in the past 28 days) or herbal medications (within 7 days).

2.1.2.2 Patients must not be on enzalutamide within five half-lives before the first planned dose of the study drug or anticipating to start enzalutamide within the next 3 months of the first planned dose of study drug

2.1.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to enzalutamide or other agents used in study.

2.1.2.4 Clinically significant cardiac disease, e.g. New York Heart Association (NYHA) classes III-IV; uncontrolled angina, uncontrolled arrhythmia or uncontrolled hypertension, myocardial infarction in the previous 6 months as confirmed by an electrocardiogram (ECG).

2.1.2.5 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

2.1.2.6 Patients who are taking medications that may alter the metabolism of enzalutamide. This includes the following: strong or moderate CYP2C8 inhibitors or inducers; strong CYP3A4 inhibitors or inducers; or CYP2C9, 2C19 or 3A4 substrates with a narrow therapeutic index. For a current table of Substrates, Inhibitors and Inducers please access the following website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

2.1.2.7 History of seizure, including any febrile seizure, loss of consciousness, or transient ischemic attach, or any condition that may pre-dispose to seizure (e.g. prior stroke,

brain arteriovenous malformation, head trauma with loss of consciousness requiring hospitalization).

2.1.3 Recruitment Strategies

This protocol may be abstracted into a plain language announcement posted on NIH websites and on NIH social media platforms. Participants will be recruited from the current patient population at NIH.

2.2 SCREENING EVALUATION

2.2.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects.
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images.
- Review of existing photographs or videos.
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes.

A waiver of consent for these activities has been requested in Section **9.6.1**.

2.2.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the subject has signed the consent for this study for screening. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a patient has signed the consent.

- **Pathological confirmation:** Patients must have histopathological documentation of prostate cancer prior to enrollment. Note: If no pathologic specimen is available, a clinical course consistent with prostate cancer is acceptable.
- **Within 8 weeks** of study entry: ECG, laboratory tests (CBC with differential and platelet count, hepatic panel, acute care panel, mineral panel, PT/PTT, serum PSA), history and physical examination with documentation of weight, and ECOG performance status.

2.3 REGISTRATION PROCEDURES

Registration will be a two-part process as patients are screened on this protocol. Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. To initially register a subject after the participant has signed the consent, complete the top portion the registration Eligibility Checklist from the website (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) indicating that the patient is being registered for screening and send via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. Once eligibility is confirmed after completion of screening studies, complete the remainder of the form which is the eligibility checklist,

indicating that the patient is being registered for treatment and email the completed registration checklist to the CRO at NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

Subjects that do not meet screening criteria should be removed from the study following the procedure in section **3.5.2**.

2.3.1 Treatment Assignment and Randomization/Stratification Procedures

Cohorts

Single Cohort study

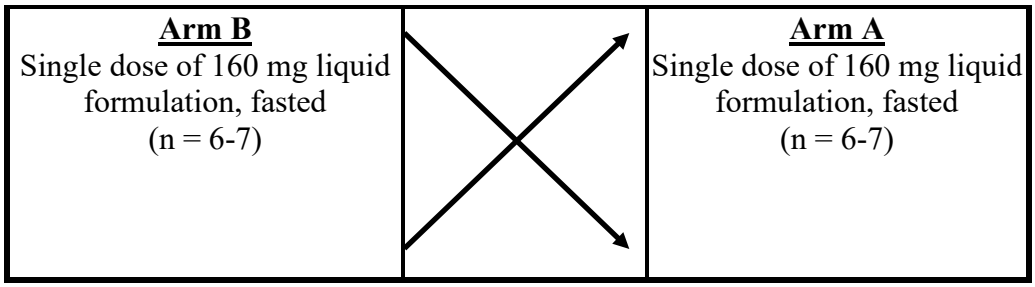
Number	Name	Description
1	Prostate Cancer	Patients with Prostate Cancer

Arms

Letter	Name	Description
A	Sequence AB	Enzalutamide capsule (Treatment A) followed by enzalutamide liquid (Treatment B)
B	Sequence BA	Enzalutamide liquid (Treatment B) followed by enzalutamide capsule (Treatment A)

Randomization and Arm Assignment

Period 1	Minimum 42-day washout	Period 2
Arm A Single dose of 4x40 mg liquid-filled capsules, fasted (n = 6-7)		**Arm B** Single dose of 4x40 mg liquid-filled capsules, fasted (n = 6-7)



Patients will be randomized on a 1:1 basis between arms A and B.

The randomization will be performed by the NCI Central Registration Office at the time of enrollment.

2.4 BASELINE EVALUATION

- History and physical examination within 17 days of treatment initiation (for medical record only).
- Laboratory studies (Tests completed at screening may be omitted if performed *within* 17 *days* of treatment initiation): **CBC with differential** and platelet count, **PT/PTT**, and **Acute care panel** (Serum sodium, Potassium test, Serum chloride, CO2, Creatinine, Glucose test, BUN); **Mineral panel** (Albumin, Calcium, Magnesium, Phosphorous – serum); **Hepatic Panel** (Alkaline phosphatase, ALT, AST, direct and total bilirubin); Gamma-GT, LDH, total cholesterol, total protein, Serum PSA, uric acid,
- Urinalysis
- Baseline ECG (within 17 days of treatment initiation)
- Vital signs including weight and height

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a randomized, open-label, single-dose, 2-way crossover, pilot bioavailability trial evaluating two oral formulations of enzalutamide. All men (n=12-14) enrolled in the trial will receive oral enzalutamide in two formulations: Treatment A will be the standard liquid-filled, soft gelatin capsule (reference) formulation; Treatment B will be the liquid formulation (test product). Subjects will be randomized in Period 1 to one of two sequences: AB or BA. Following a minimum 42-day washout period, subjects will be crossed over in Period 2 to receive the treatment that they did not receive in Period 1. Blood samples will be collected for pharmacokinetic analysis.

Subjects are admitted to the Clinical Center on Day 1 (for the first 24-hours of PK sampling) and will take a single 160mg dose of enzalutamide. They are to return to the Clinical Center on Day 3 for the 48h, on Day 8 for the 168h, and Day 42 for the post-dose blood draws. After an appropriate washout period (at least 42 days), subjects will be crossed over in Period 2 to receive the treatment that they did not receive in Period 1. Subjects will be re-admitted to the Clinical Center to receive the study drug and blood samples will be drawn as described above on Days 1, 3, 8, and 42.Drug Administration

3.2 DRUG ADMINISTRATION

Enzalutamide will be administered under the following fasting conditions (no caloric intake for 2 hours before dosing and 2 hours after dosing).

Subjects will be randomized in Period 1 to one of two sequences: AB or BA. Subjects are admitted to the Clinical Center on Day 1 (for the first 24-hours of PK sampling) and will take a single 160mg dose of an oral enzalutamide formulation. After an appropriate washout period (at least 42 days), subjects will be crossed over in Period 2 to receive the treatment that they did not receive in Period 1. Subjects will be re-admitted to the Clinical Center to take another 160mg dose of an oral enzalutamide formulation.

Enzalutamide will be administered at approximately 0800 hours with ambient temperature water to a total volume of about 240 mL. When the liquid formulation is administered, the subject will administer the liquid directly from the oral syringe into the mouth and will swallow. Following administration of the liquid dose, a small volume of water (e.g. 3-7 mLs) may be drawn into the syringe and then the contents will be administered orally to the subject. This technique to "rinse" the syringe is intended to reduce the residual enzalutamide remaining in the oral syringe to ensure the complete dose is administered. This will be followed by approximately 240 mL water. When the capsule formulation is administered, capsules must be swallowed whole without breaking, crushing, or chewing with approximately 240 mL water.Subjects are required to refrain from drinking beverages other than water or eating for 2 hours after dosing. Subjects may resume their normal meals 2 hours after dosing.

3.3 STUDY CALENDAR

Procedure	Screening	Baseline	Period 1					Period 2				
			Day 1	Day 2	Day 3	Day 8	Day 42	Day 1	Day 2	Day 3	Day 8	Day 42
Confirmation of diagnosis	X	X										
History and PE	X	X	X[g]				X	X[d]				X
Vital signs	X	X	X			X	X	X[d]				X
Performance Score	X	X					X	X[d]				X
Labs	X[a]	X[b]	X[f]				X	X[d]				X
Urinalysis	X	X					X	X[d]				X
ECG	X	X					X	X[d]				X
PK[c]	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X	X
Concomitant Medications			X			X	X	X[d]			X	X
Questionnaire			X[e]					X[e]				

[a]For screening labs see Section **2.2**

[b]For baseline labs see Section **2.4**;

[c]See Section **5.1** for complete details.

[d]With the exception of PK and adverse events, all assessments and labs on Period 2 Day 1 do not need to be repeated if within 8 days of Period 1 Day 42.

[e]Subjects will be given a questionnaire (see **APPENDIX B**) to complete following the administration of the liquid (test) formulation to assess the tolerability. The questionnaire is only completed on the day the liquid formulation is administered. It is not necessary to complete the quiestionnaire on the day the capsule formulation is administered.

[f]Labs do not need to be repeated if they were completed at screening/baseline within 17 days of of period 1 day 1.

[f]H&P may be performed within 17 days of treatment initiation.

3.4 COMPENSATION

Study participants will be compensated for each blood sample collected for PK analysis as follows:

- $20 for the 1st pre-dose (0 hour) PK sample
- $20 for the 2nd (30 minutes post dose) PK sample
- $20 for the 3rd (1 hour post dose) PK sample
- $20 for the 4th (2 hours post dose) PK sample
- $20 for the 5th (4 hours post dose) PK sample
- $20 for the 6th (8 hours post dose) PK sample
- $20 for the 7th (24 hours post dose) PK sample
- $20 for the 8th (48 hours post dose) PK sample
- $20 for the 9th (168 hours post dose) PK sample
- $20 for the 10th (Day 42 post dose) PK sample

All remuneration will be directed to be paid to the participant via check through standard compensation procedures. These funds are intended to compensate for time away from work that is required to participate in this study. As we intend to recruit from the local metropolitan region, we will not provide remuneration for meals, lodging or transportation. If a participant withdraws from study, no future compensation will be made, but prior compensation will not be revoked.

Subjects will not receive direct benefit from their study participation in this protocol.

Subjects will only be compensated if samples are collected solely for research purposes.

If subjects return to clinic solely for any clinical/non-research reasons, subjects will not be reimbursed.

3.5 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

3.5.1 Criteria for removal from protocol therapy

- Completion of protocol therapy
- Participant requests to be withdraw from active therapy
- Unacceptable Toxicity as determined by the investigator
- Investigator discretion

3.5.2 Off-Study Criteria

- Completed study follow-up period
- Participant requests to be withdrawn from study
- Loss of capacity to render informed consent
- Death
- Screen failure

3.5.3 Off Protocol Therapy and Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol therapy and when a subject is taken off-study. A Participant Status Updates Form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

4 CONCOMITANT MEDICATIONS/MEASURES

Patients may be on concomitant drugs to prevent bone loss, including calcium, vitamin D, bisphosphonates and denosumab.

Other supportive care with blood components, antibiotics, analgesics, general medical therapy, etc., will be delivered as required.

4.1 GENERAL GUIDELINES

All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) taken within 28 days of starting study treatment through the follow up visit should be reported on the CRF.

While patients are on protocol treatment, all medications required for the health of the patient are allowed with the following exception: concomitant use of herbal supplements.

4.2 SEIZURE THRESHOLD LOWERING DRUGS

Use caution when coadministering medications which may lower the seizure threshold.

4.3 CYTOCHROME P450 AND P-GLYCOPROTEIN

- Co-administration of enzalutamide with strong or moderate CYP2C8 inducers (e.g., rifampin) or inhibitors may alter the plasma exposure of enzalutamide and are not allowed while on study.
- Co-administration of enzalutamide with strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) or inhibitor may alter the plasma exposure of enzalutamide and are not allow while on study. Selection of a concomitant medication with no or minimal CYP3A4 induction potential is recommended.
- Moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) and St. John's Wort may also reduce the plasma exposure of enzalutamide and should be avoided if possible.
- Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin), or CYP2C19 (voriconazole) should be avoided, as enzalutamide may decrease their exposure.
- Grapefruit, Seville oranges, and starfruit affect P450 and PgP activity. Concomitant use should be avoided.

5 BIOSPECIMEN COLLECTION

5.1 CORRELATIVE STUDIES FOR RESEARCH/PHARMACOKINETIC STUDIES

The time of enzalutamide dose administration is t = 0 for purposes of pharmacokinetic sample collection times. Due to the long t½ of enzalutamide, *N*-desmethyl enzalutamide, and the carboxylic acid metabolite in healthy subjects (approximately 6, 8, and 10 days, respectively [7], pharmacokinetic samples will be collected over 42 days.

With each 160 mg dose of enzalutamide, pharmacokinetic blood samples will be collected in 6-mL tubes with dipotassium ethylenediaminetetraacetic acid (K2 EDTA) as the anticoagulant. Venous blood samples for plasma will be collected at the following times: pre-dose (0 hr) and post-dose at 30 minutes; and at 1, 2, 4, and 8 hours (Day 1), 24h (Day 2), 48h (Day 3), 168h (Day 8), and Day 42 post-dose.

Validated bioanalytical methods based on ultra high-performance liquid chromatography with tandem mass spectrometry (uHPLC-MS/MS) [10] will be developed by the Clinical Pharmacology Program and used to analyze plasma samples for concentrations of enzalutamide and the two major human metabolites (e.g. *N*-desmethyl enzalutamide and carboxylic acid enzalutamide).

Non-compartmental PK analysis of enzalutamide in plasma will be performed using WinNonlin 5.0 (Pharsight, Inc., Mountain View, CA). PK parameters derived from plasma concentration-time data may include C_{max}, T_{max}, AUC, Cl, Cl/F, Vd, and $t_{1/2}$.

5.2 SAMPLE PROCESSING

All samples will be sent to and stored in Dr. Figg's Lab at NCI, Bldg 10, Bethesda, MD. Place all samples on wet ice.

Please e-mail NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov.

5.3 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

Any transfer of materials to other NIH or non-NIH investigators will occur following NIH Intramural Research Program guidelines. If the subject withdraws consent the participants data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

Upon arrival in the Clinical Pharmacology Program (CPP), blood samples will be centrifuged and the plasma transferred into cryovials for storage at -80° C until the time of analysis.

All PK samples will be barcoded, with data entered and stored in the LABrador (aka LabSamples) utilized by the CPP. This is a secure program, with access to LABrador System limited to defined CPP personnel, who are issued individual user accounts. The program creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients with LABrador access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer locations. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (e.g. delay in sample processing, storage conditions on the ward, etc.).

Barcoded samples are stored in barcoded boxes in locked freezers at either -20 C or -80 C according to stability requirements. These freezers are located onsite in the CPP and offsite at NCI Frederick Central Repository Services in Frederick, MD. Samples will be stored until requested by a researcher named on the protocol.

All requests are monitored and tracked in LABrador. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per IRB approved protocol) and that any unused samples must be returned to the CPP.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. The PI will record any loss or unanticipated descruction of samples as a deviation. Reporting will be per the requirments of Section **7.2**.

Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the LABrador. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate pharmacokinetic data with these variables.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

C3D and LABrador will be used for data collection purposes. The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in Section **7.2.1**.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

- Coded, linked data in an NIH-funded or approved public repository.
- Coded, linked data in BTRIS (automatic for activities in the Clinical Center)

How and where will the data be shared?

Data will be shared through:

- An NIH-funded or approved public repository. Insert name or names: ClinicalTrials.gov .
- BTRIS (automatic for activities in the Clinical Center)
- Approved outside collaborators under appropriate individual agreements.
- Publication and/or public presentations.

When will the data be shared?

- Before publication.
- At the time of publication or shortly thereafter.

6.3 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here.

7.3 FDA REQUIREMENTS

The person conducting the study must retain reserve samples of any test article and reference standard used in the study and release the reserve samples to FDA upon request, in accordance with, and for the period specified in, 320.38 (at least 5 years following the date of completion of the bioavailability study in which the sample from which the reserve sample was obtained was used).

The PI or AI must notify FDA and all participating investigators of any serious adverse event, observed during the conduct of the study as soon as possible but in no case later than 15 calendar days after becoming aware of its occurrence. Each report must be submitted on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. Each report must bear prominent identification of its contents, i.e., "bioavailability/bioequivalence safety report." The person conducting the study must also notify FDA of any fatal or life-threatening adverse event from the study as soon as possible but in no case later than 7 calendar days after becoming aware of its occurrence. Each notification under this paragraph must be submitted to the Director, Office of Generic Drugs in the Center for Drug Evaluation and Research at FDA. Relevant followup information to a bioavailability/bioequivalence safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Followup bioavailability/bioequivalence safety report." Upon request from FDA, the person conducting the study must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

7.4 NCI CLINCIAL DIRECTOR RERPORTING

Problems expeditiously reported to the OHSRP in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.5 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.5.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis (at least weekly) when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in Section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL HYPOTHESES

Primary efficacy endpoints:

To evaluate the bioequivalence of two oral formulations of enzalutamide following a single 160 mg dose in male subjects with prostate cancer.

The primary measure of efficacy will be AUC for the first period of administration obtained during blood draws during visits on day 1, 3, 8, and 42 evaluations, and then AUC at a second set of visits at least 42 days after the first administration, for evaluations on days 1, 3, 8 and 42 relative to the second administration, for the second period evaluations.

Secondary efficacy endpoints:

To evaluate the safety and tolerability of two oral formulations of enzalutamide following a single 160 mg dose in male subjects with prostate cancer.

8.2 SAMPLE SIZE DETERMINATION

This study will be conducted as a two-period randomized crossover trial design. Patients will be randomized to initially receive the standard liquid filled soft gelatin formulation (Arm A) followed later by the liquid formulation, or the liquid formulation as the test product (Arm B)

followed by the liquid filled soft gelatin formulation. A total of 12 evaluable patients will be randomized into the two arms. It has been identified that a decrease of approximately 30-40 ug*h/mL in the AUC (less than a 20% decrease in the AUC for the test version vs. the standard formulation) would permit the two formulations to be considered bioequivalent, and it may be expected that the actual difference between the formulations may be a decline of approximately 10% (approximately 20 ug*h/mL). When the sample size in each sequence arm is 6, (a total sample size of 12) a crossover design will have 80% power to reject the null hypothesis that the Arm B mean minus the Arm A mean is below -40 ug*h/mL and the null hypothesis that the Arm B mean minus the Arm A mean is above 0 ug*h/mL, i.e., that the two groups are not equivalent, in favor of the alternative hypothesis that the means of the two treatments are equivalent, assuming that the expected difference in means is -20 ug*h/mL, the standard deviation of differences, s_d, is 20 ug*h/mL, and that each test is made at the 5% level.

It is expected that approximately 1 patient per month may enroll onto this trial. Thus, to enroll 12 evaluable patients, it is anticipated that one year may be required. To allow for the possibility of a small number of patients who do not have full measurements obtained based on both drug administrations, the accrual ceiling will be set at 14 patients.

8.3 POPULATIONS FOR ANALYSIS

Modified intention to treat. Only patients who participated in both drug administrations and have blood draws on at least 3 of the 4 required dates for each of the two administrations.

8.4 STATISTICAL ANALYSES

8.4.1 General Approach

The difference in the AUCs will be calculated following a published non-parametric approach for analyzing data from two-period cross-over studies:

Koch GG "The Use of Non-parametric methods in the statistical analysis of the two-period change-over design. *Biometrics* 28: 577-584 (1972).

8.4.2 Analysis of the Primary Efficiacy Endpoints

The average of the AUC values at the 4 determinations associated with each of the two drug administrations will be determined and the difference assessed for statistical significance at the 0.05 level using the non-parametric procedures identified in the Koch 1972 paper.

8.4.3 Analysis of the Secondary Efficacy Endpoints

The number of episodes of nausea and vomiting, as well as the grades of nausea and vomiting will be calculated and reported for each of the two formulations at each time point. The rates of grade 3 vomiting will be compared between the two formulations at each time point using Fisher's exact test.

8.4.4 Safety Analyses

Toxicity data: tabulated counts. The primary toxicity, nausea and vomiting, will be reported per arm at each of the time points when the drugs are administered.

8.4.5 Baseline Descriptive Statistics

Demographic and clinical characteristics of patients on both arms will be tabulated.

8.4.6 Planned Interim Analyses

No interim analyses are planned; the data will be analyzed at the completion of the trial.

8.4.7 Subgroup Analyses

None will be performed; inadequate numbers of subjects to be enrolled for meaningful subgroup analyses.

8.4.8 Tabulation of Individual Participant Data

None will be provided

8.4.9 Exploratory Analyses

There are no exploratory objectives so no exploratory analyses will be undertaken.

9 HUMAN SUBJECTS PROTECTIONS

9.1 RATIONALE FOR SUBJECT SELECTION

9.1.1 Selection Based on Ethnicity, and Race

Subjects from all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. To date, there is no information that suggests that differences in drug metabolism or disease response would be expected in one group compared with another. Efforts will be made to extend accrual to a representative population, but in this preliminary study, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic and/or ineffective treatments on one hand and the need to explore ethnic aspects of clinical research on the other hand. If differences in outcome that correlate with ethnic identity are noted, accrual may be expanded or a follow-up study may be written to investigate those differences more fully. Women are not eligible for this protocol as this disease occurs only in men.

9.1.2 Strategies/Procedures for Recruitment

Patient accrual for this protocol will be facilitated by Web-based recruitment strategies. This protocol will be listed on clinicaltrials.gov.

9.2 PARTICIPATION OF CHILDREN

Because no dosing or adverse event data are currently available on the use enzalutamide in patients <18 years of age and because prostate cancer is uncommon in pediatric populations, children are excluded from this study, but may be eligible for future pediatric trials.

9.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol because there is no prospect of direct benefit. Adults who become incapacitated or cognitively impaired during the course of the study will be removed from the study.

9.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

9.4.1 Alternative Approaches or Treatments

Patients will be consented verbally and in writing regarding the risks and benefits of this trial, the treatment requirements, and alternative approaches to entering on this trial.

9.4.2 Procedure for Protecting Against or Minimizing any Potential Risks

All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. This study may involve risks to patients, which are currently unforeseeable. All patients will have blood tests, examinations and scans as described in the protocol evaluation (Section **3.3**, Study Calendar). Patients will also be required to have a local physician to provide long-term care and to monitor for complications. If patients suffer any physical injury as a result of the participation in this study, immediate medical treatment is available at the Clinical Center, National Cancer Institute, Bethesda, Maryland. Although no compensation is available, any injury will be evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

9.4.3 Provisions for Monitoring Data Collection to Ensure Safety of Subjects

As information is gathered from this trial, clinical results will be shared with patients as they become available. Laboratory and clinical data will be frequently gathered and any new significant finding(s) found during the course of the research, which may affect a patient's willingness to participate further, will be explained. Confidentiality of information concerning participants will be maintained, including in all publications and presentations results from this study. Names of participants and/or material identifying participants will not be released without permission, except as such release is required by law. Records at the National Cancer Institute are maintained according to current legal requirements, and are made available for review, as required by the Food and Drug Administration or other authorized users, only under the guidelines established by the Federal Privacy Act.

9.5 RISKS/BENEFITS ANALYSIS

<u>Adult Subjects</u>

The patient will derive no direct benefit from the procurement of blood or from the enzalutamide as administered in this protocol and this will be clearly stated in the protocol consent.

The risks of blood draw are relatively small and include pain at the needle site, bruising, possible dizziness if you stand up quickly, and possible inflammation of the vein or infection at the needle site.

The dose (160mg) and route of administration (oral) of enzalutamide being used in this study has been approved by the FDA for the treatment of prostate cancer. However, the safety of

administering the enzalutamide liquid without the capsule surround has not been evaluated. The potential risk of the liquid formulation which may be greater than the capsule formulation include local irritation effects and accidental aspiration.

9.6 CONSENT PROCESS AND DOCUMENTATION

The investigational nature and objectives of this trial, the procedures involved, and their attendant risks and discomforts, potential benefits, and potential alternative therapies will be explained to the patient and a signed informed consent document obtained. Moreover, any experimental invasive procedure will require a separate consent form. All associate investigators who have clinical privileges listed in this protocol are permitted to obtain informed consent.

9.6.1 Request for Waiver of Consent for Screening Activities

Prior to the subject signing the consent for this study pre-screening activities listed in Section **2.2.1** may be performed.

We request a waiver of consent for these activities as they involve only minimal risk to the subjects. A waiver will not adversely affect the rights and welfare of the subjects given that the activities are only intended to determine suitability for screening for participation in research protocols. These activities could not practicably be carried out without the wavier as central recruiting services, utilized in the NIH Clinical Center, perform pre-screening activities for multiple studies and obtaining consent for each one is beyond their resources. The subjects will be provided with additional pertinent information after participation as they will be informed whether or not they are eligible to sign a consent for additional screening.

9.6.2 Telephone Re-consent

In the cases where re-consent is needed, re-consent may be obtained via telephone.

Telephone consent will be obtained and documented per OHSRP/IRBO and CCR policies and procedures.

10 PHARMACEUTICAL INFORMATION

This study meets the criteria for exemption from IND based on the following criteria listed in Title 21 Code of Federal Regulations:

- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug;
- The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
- The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50); and
- The investigation is conducted in compliance with the requirements of 312.7

10.1 ENZALUTAMIDE

10.1.1 Source

Enzalutamide will be obtained from commercial sources and dispensed by the institutional pharmacy.

10.1.2 Toxicity

10.1.2.1 Seizure

In the randomized clinical trial, 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. 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 past 12 months, cerebral vascular accident, brain metastases, brain arteriovenous malformation or the use of concomitant medications that may lower the seizure threshold. Because of the risk of seizure associated with enzalutamide use, patients should be advised of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.

10.1.2.2 Other adverse events

The most common adverse drug reactions (≥ 5%) reported in patients receiving enzalutamide in the randomized clinical trial 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. Grade 3 and higher adverse reactions were reported among 47% of enzalutamide-treated patients and 53% of placebo-treated patients. 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 compared to none (0%) of the placebo-treated patients. Hypertension was also seen in patients who received enzalutamide relative to placebo (6.6% vs. 3.3%).

10.1.2.3 Laboratory Abnormalities

In the randomized clinical trial, Grade 1-4 neutropenia occurred in 15% of patients on enzalutamide (1% Grade 3-4) and in 6% of patients on placebo (no Grade 3-4). The incidence of Grade 1-4 thrombocytopenia was similar in both arms; 0.5% of patients on enzalutamide and 1% on placebo experienced Grade 3-4 thrombocytopenia. Grade 1-4 elevations in ALT occurred in 10% of patients on enzalutamide (0.3% Grade 3-4) and 18% of patients on placebo (0.5% Grade 3-4). Grade 1-4 elevations in bilirubin occurred in 3% of patients on enzalutamide and 2% of patients on placebo.

10.1.2.4 Infections

In the randomized clinical trial, 1.0% of patients treated with enzalutamide compared to 0.3% of patients on placebo died from infections or sepsis. Infection-related serious adverse events were reported in approximately 6% of the patients on both treatment arms.

10.1.2.5 Falls and Fall-related Injuries

In the randomized clinical trial, falls or injuries related to falls occurred in 4.6% of patients treated with enzalutamide compared to 1.3% of patients on placebo. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in patients treated with enzalutamide and included non-pathologic fractures, joint injuries, and hematomas.

10.1.2.6 Hallucinations

In the randomized clinical trial, 1.6% of patients treated with enzalutamide were reported to have Grade 1 or 2 hallucinations compared to 0.3% of patients on placebo. Of the patients with hallucinations, the majority were on opioid-containing medications at the time of the event. Hallucinations were visual, tactile, or undefined.

10.1.3 Formulation and Preparation

Enzalutamide (XTANDI ©) is an androgen receptor inhibitor. The chemical name is 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5- dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}z-2-fluoro-*N*-methylbenzamide. Enzalutamide is a white crystalline non-hygroscopic solid. It is practically insoluble in water.

10.1.3.1 Standard (reference) Formulation

Enzalutamide is provided as liquid-filled soft gelatin capsules for oral administration. Each capsule contains 40 mg in 0.96 mL of enzalutamide as a solution (unpublished) in caprylocaproyl polyoxylglycerides. The inactive ingredients are caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, and black iron oxide.

10.1.3.2 Liquid (test) Formulation

The liquid (test) formulation of enzalutamide is prepared by extracting the liquid from the gelatin capsule by pharmacy personnel in a biological safety cabinet or appropriate clean bench. The soft gelatin enzalutamide capsule (which contains 40 mg in 0.96 mL) will be cut using a sharp object (scissor or similar item). Then, using a needle, the appropriate amount of liquid will be extracted from the necessary number of capsules to equal a 160mg dose. The liquid formulation will be stored at room temperature and given a 24 hour expiration from the time of preparation and will then be dispensed in a Baxter EXACTAMED oral 10mL amber syringe for oral administration.

10.1.4 Stability and Storage

Store enzalutamide capsules between 20°C to 25°C (68°F to 77°F) in a dry place and keep the container tightly closed. Excursions permitted from 15°C to 30°C (59°F to 86°F). The expiration date for each lot utilized in this study will be obtained from commercial packaging.

Stability studies have been completed after 24 hours for the liquid enzalutamide after it has been extracted from the capsule. The concentration of enzalutamide extracted from the capsule at time 0 was compared to the concentration of enzalutamide at 24 hours post extraction. During the 24 hour period, liquid enzalutamide was stored in Baxter EXACTAMED oral 10mL amber syringes. The enzalutamide concentration at 24 hours post extraction decreased by 3.04% indicating stability at this time point (a concentration +/- 10% from time 0 was concerned acceptable). Additional stability studies are ongoing.

10.1.5 Administration Procedures

Enzalutamide will be administered under fasting conditions (no caloric intake for 2 hours before dosing and 2 hours after dosing) as a liquid formulation (as prepared by extracting the liquid as described in Section **10.1.3.2**) and liquid-filled, soft gelatin capsules (4 x 40mg capsules, 160mg total). When the liquid formulation is administered, the subject will administer the liquid directly from the oral syringe into the mouth and swallow. Following administration of the liquid dose, a small volume of water (e.g. 3-7 mLs) may be drawn into the syringe and then the contents will be administered orally to the subject. This technique to “rinse” the syringe is intended to reduce the residual enzalutamide remaining in the oral syringe to ensure the complete dose is administered. This will be followed by approximately 240 mL water. When the capsule formulation is administered, capsules must be swallowed whole without breaking, crushing, or chewing with approximately 240 mL water.

10.1.6 Tolerability Assessment

To date, there is no available information on the palatability of the liquid enzalutamide preparation. Therefore, a brief tolerability assessment will be completed by each participant. Following the administration of the liquid (test) formulation, participants will be asked to complete APPENDIX B

11 REFERENCES

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12 APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

13 APPENDIX B*:* TOLERABILITY ASSESSMENT OF LIQUID (TEST) ENZALUTAMIDE FORMULATION

The following questions refer to the liquid enzalutamide formulation you took.

1. Did you complete taking the liquid enzalutamide formulation? (circle one)

   yes no

   If no, why did you not complete taking the medication?

   _____

2. Please rate the overall taste of the liquid enzalutamide formulation. (circle one)

   bad almost acceptable acceptable good

3. Which of the following best describes the taste of the liquid enzalutamide formulation? (circle one)

   sweet salty bitter other (please describe below)

   _____

4. Did you encounter any problems with the use of this liquid formulation?

   yes no

   If yes, please describe what problems you encountered:

   _____

5. In your opinion, would the liquid formulation be an acceptable way of taking enzalutamide if you had difficulty swallowing? (circle one)

   yes no