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CLINICAL STUDY PROTOCOL	
TITLE	A Phase 1b Safety and Tolerability Study of ZEN003694 in Combination with Enzalutamide or Abiraterone in Patients with Metastatic Castration-Resistant Prostate Cancer
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PROTOCOL NUMBER	ZEN003694-002
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LIST OF ABBREVIATIONS AND ACRONYMS

5-HT3	5-hydroxytryptamine type 3
ADL	Activities of daily living
ADT	Androgen deprivation therapy
AE	Adverse event
AML	Acute myeloid leukemia
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Androgen receptor
ARSI	Androgen receptor signaling inhibitor
AR-V7	Androgen receptor splice variant 7
ASCO	American Society of Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0-\infty}$	Area under the curve, from time zero to infinity
AUC_{0-24}	Area under the curve, from time zero to 24 hours
AUC_{0-last}	Area under the curve, from time zero to last time point with a quantifiable level of drug
BCL-2	B-cell lymphoma 2
BCL2L1	B-cell lymphoma 2-like 1
BET	Bromodomain and extra-terminal motif
BETi	BET bromodomain inhibitor
BID	Twice Daily
BRD2	Bromodomain-containing protein 2
BRD3	Bromodomain-containing protein 3
BRD4	Bromodomain-containing protein 4
BRDT	Bromodomain-testis-specific containing protein T
BUN	Blood urea nitrogen
C_{max}	Maximum or peak concentration
C_{min}	Minimum or trough concentration
C_{ss}	Concentration steady-state
CBC	Complete blood count
CCR1	Chemokine (C-C motif) receptor 1
CDMS	Clinical data management system
cfDNA	Cell-free deoxyribonucleic acid (DNA)
[redacted]	[redacted]
CNS	Central nervous system
CR	Complete response
CRC	Cohort Review Committee
CRF	Case report form
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
CTC(s)	Circulating tumor cell(s)
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor deoxyribonucleic acid (DNA)

CYP	Cytochrome P450
CYP1A2	Cytochrome P450, family 1, subfamily A, polypeptide 2
CYP2C8	Cytochrome P450, family 2, subfamily C, polypeptide 8
CYP2C9	Cytochrome P450, family 2, subfamily C, polypeptide 9
CYP2C19	Cytochrome P450, family 2, subfamily C polypeptide 19
CYP3A4	Cytochrome P450, family 3, subfamily A, polypeptide 4
CYP17A1	Cytochrome P450, family 17, subfamily A, polypeptide 1, or steroid 17-alpha-hydroxylase/17,20 lyase
DC	Dose confirmation
DE	Dose escalation
dL	Decilitre
DLT	Dose-limiting toxicity
DMP	Data management plan
[redacted]	[redacted]
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ERG	V-Ets avian erythroblastosis virus E26 oncogene
ETS	E26 transformation-specific
ETV1	ETS translocation variant 1
FDA	Food and Drug Administration
FIH	First-in-human
[redacted]	[redacted]
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GPR183	G Protein-Coupled Receptor 183
GR	Glucocorticoid receptor
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HED	Human equivalent dose
hERG	Human ether-à-go-go related gene (an ion channel found in cardiac cell membranes)
HIST2H2BE	Histone gene cluster 1, H2BE histone family member E
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
HRR	Hardy Rand and Rittler (plates for testing color vision)
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IL1RN	Interleukin 1 receptor antagonist
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram(s)

L	Litre
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LD	Longest diameter
LDH	Lactate dehydrogenase
mCRPC	Metastatic castration-resistant prostate cancer
mg	Milligram(s)
min	Minute(s)
mm^3	Cubic milimeter
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
msec	Millisecond(s)
MTD	Maximum tolerated dose
MUGA	Multigated acquisition (scan)
MYC	V-Myc avian myelocytomatosis viral oncogene homolog
NCI	National Cancer Institute
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
ng	Nanogram(s)
OCT	Optical Coherence tomography
PCWG2	Prostate Cancer Working Group 2
PD	Pharmacodynamics
PD	Progressive disease
PK	Pharmacokinetics
PR	Partial response
PRES	Posterior reversible encephalopathy syndrome
PSA	Prostate-specific antigen
PT	Prothrombin time
PTT	Partial thromboplastin time
QD	Once daily
qPCR	Quantitative polymerase chain reaction
QTcF	QT interval corrected by the Fridericia correction formula
RP2D	Recommended Phase 2 dose
RECIST 1.1	Response Evaluation Criteria in Solid Tumors 1.1
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
STD_{10}	Severely toxic dose in approximately 10% of animals
SUSAR	Suspected unexpected serious adverse event
$t_{1/2}$	Half-life
Tech-99	Technetium-99
T_{max}	Time to maximum concentration
TGI	Tumor growth inhibition
ULN	Upper limit of normal

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1. SYNOPSIS

TITLE: A Phase 1b Safety and Tolerability Study of ZEN003694 in Combination with Enzalutamide or Abiraterone in Patients with Metastatic Castration-Resistant Prostate Cancer

PROTOCOL NUMBER: ZEN003694-002

STUDY PHASE: Phase 1

INVESTIGATIONAL DRUG: ZEN003694

OBJECTIVES:

Part 1: ZEN003694 in combination with enzalutamide

Primary

- To determine the safety, tolerability and maximum tolerated dose (MTD) of ZEN003694 in combination with enzalutamide or apalutamide in patients with metastatic castration-resistant prostate cancer (mCRPC) who have progressed during prior treatment with enzalutamide or apalutamide (Cohort DE-A) or abiraterone (Cohort DE-B) by Prostate Cancer Working Group 2 (PCWG2) criteria 2007 (dose escalation)
- To confirm the safety and tolerability of the MTD and recommended Phase 2 dose (RP2D) of ZEN003694 in combination with enzalutamide in the following two cohorts of patients with mCRPC (dose confirmation):
    - Cohort DC-A: Patients with prior progression on enzalutamide or apalutamide by PCWG2 criteria who are currently or will be receiving a stable dose of enzalutamide
    - Cohort DC-B: Patients who are enzalutamide-naïve and apalutamide-naive with prior progression on abiraterone by PCWG2 criteria

Secondary

- To determine the pharmacokinetics (PK) of ZEN003694 and the PK of enzalutamide along with their primary active metabolites when administered in combination
- To evaluate the preliminary clinical activity of ZEN003694 in combination with enzalutamide as applicable:
    - PSA response rate by PCWG2 criteria
    - Radiographic response rate by PCWG2 criteria
    - Median progression-free survival by PCWG2 criteria
    - Circulating tumor cell (CTC) response rate (dose confirmation only)

Exploratory

- To explore pharmacodynamics (PD), prognostic and/or predictive biomarkers of ZEN003694 in combination with enzalutamide in whole blood, plasma and tumor samples in the dose escalation phase and/or dose confirmation phase as follows:
    - Possible relationship of baseline tumor abnormalities (such as mutations,

translocations, messenger ribonucleic acid [mRNA], protein expression and localization), in circulating tumor DNA (ctDNA), circulating tumor cells (CTC) and tumor biopsies and/or on-treatment changes with any observed antitumor activity

- To explore the effects of ZEN003694 on immuno-oncology markers in tumor tissue and peripheral blood mononuclear cells

Part 2: ZEN003694 in combination with abiraterone

Primary

- To determine the safety, tolerability and recommended Phase 2 dose (RP2D) of ZEN003694 in combination with abiraterone in patients with metastatic castration-resistant prostate cancer (mCRPC) who have progressed during prior treatment with abiraterone (Cohort DE-C) or enzalutamide or apalutamide (Cohort DE-D) by Prostate Cancer Working Group 2 (PCWG2) criteria 2007 (Dose Escalation)

- To confirm the safety and tolerability of the recommended Phase 2 dose (RP2D) of ZEN003694 in combination with abiraterone in the following two cohorts of patients with mCRPC (dose confirmation):

    - Cohort DC-C: Patients currently receiving abiraterone who have experienced progression by PCWG2 criteria

    - Cohort DC-D: Patients who are abiraterone-naïve with prior progression on enzalutamide or apalutamide by PCWG2 criteria

Secondary

- To determine the pharmacokinetics (PK) of ZEN003694 and the PK of abiraterone along with their primary active metabolites when administered in combination

- To evaluate the preliminary clinical activity of ZEN003694 in combination with abiraterone as applicable:
    - PSA response rate by PCWG2 criteria
    - Radiographic response rate by PCWG2 criteria
    - Median progression-free survival by PCWG2 criteria
    - Circulating tumor cell (CTC) response rate (dose confirmation only)

Exploratory

- To explore pharmacodynamics (PD), prognostic and/or predictive biomarkers of ZEN003694 in combination with abiraterone in whole blood, plasma and tumor samples in the dose escalation phase and/or dose confirmation phase as follows:

    - Possible relationship of baseline tumor abnormalities (such as mutations, translocations, messenger ribonucleic acid [mRNA], protein expression and localization), in circulating tumor DNA (ctDNA), circulating tumor cells (CTC) and tumor biopsies and/or on-treatment changes with any observed antitumor activity

STUDY DESIGN:

This is an open label, non-randomized, Phase 1 dose escalation/dose confirmation study of ZEN003694 in combination with enzalutamide (Part 1) and abiraterone (Part 2) in patients with mCRPC.

Dose Escalation

A standard 3+3 cohort design will be utilized for each study Part. Cohorts of up to 6 patients will be enrolled at each dose level, and each patient will participate in only one cohort. Each cycle will be 28 days in duration.

Part 1, ZEN003694 in combination with enzalutamide:
For patients who have progressed on abiraterone (Cohort DE-B), enzalutamide will be administered orally as a single agent daily for 14 days prior to the initiation of the combination therapy (Lead-in) to reach enzalutamide steady-state concentration (C_{ss}) during Cycle 1. After the Lead-in, if applicable, ZEN003694 will be administered orally in combination with daily enzalutamide for 28-day cycles. Patients who are progressing on enzalutamide or apalutamide (Cohort DE-A, Sub-Arm A1) and currently receiving a stable dose of enzalutamide will continue to receive enzalutamide in combination with ZEN003694, if eligibility criteria are met. For patients who have progressed on enzalutamide or apalutamide (Cohort DE-A, Sub-Arm A2) but are not currently taking enzalutamide or apalutamide or are currently taking apalutamide, enzalutamide will be administered orally as a single agent daily for 14 days prior to the initiation of the combination therapy (Lead-in) to reach enzalutamide steady-state concentration (C_{ss}) during Cycle 1.

Part 2, ZEN003694 in combination with abiraterone:
For patients who have progressed on enzalutamide or apalutamide (Cohort DE-D), abiraterone will be administered orally as a single agent daily for 14 days prior to the initiation of the combination therapy (Lead-in) to reach abiraterone steady-state concentration (C_{ss}) during Cycle 1. After the Lead-in, if applicable, ZEN003694 will be administered orally in combination with daily abiraterone for 28-day cycles. Patients who are progressing on abiraterone (Cohort DE-C, Sub-Arm C1) and currently receiving a stable dose of abiraterone will continue to receive abiraterone in combination with ZEN003694, if eligibility criteria are met. For patients who have progressed on abiraterone (Cohort DE-C, Sub-Arm C2) but are not currently taking abiraterone, abiraterone will be administered orally as a single agent daily for 14 days prior to the initiation of the combination therapy (Lead-in) to reach abiraterone steady-state concentration (C_{ss}) during Cycle 1.

Part 1 and Part 2:
After the Lead-in, if applicable, ZEN003694 will be administered orally in combination with daily enzalutamide (Part 1) or abiraterone (Part 2) for 28-day cycles. The first patient at each dose level will be treated with ZEN003694 for one week before the second patient at the same dose level is allowed to receive their first dose of ZEN003694. Patients at each dose level will be treated (for 28 days on ZEN003694) and observed through the end of the first cycle before treatment of patients at the next higher dose level can begin. If alternative dosing regimens are explored, the one week delay of enrollment between the first and subsequent patients may be waived by the Cohort Review Committee (CRC) as long as the daily exposure is known to be tolerated.

ZEN003694-related adverse events (AEs) for determination of DLTs will be assessed for each patient during the 28 days of Cycle 1. The most common AEs for enzalutamide and abiraterone are well-known. As such, the Investigator should to the best of his/her ability assess the relatedness of an AE observed as attributable to either enzalutamide (Part 1) or abiraterone (Part 2) or ZEN003694

alone, or if unable to do so, as attributable to the combination of enzalutamide (Part 1) or abiraterone (Part 2) and ZEN003694.

Dose escalation will continue after all patients enrolled within a cohort have completed the 28-day Cycle 1 DLT observation period with either 0 of 3 patients, or no more than 1 out of 6 patients in a cohort experiencing a DLT, with the proviso that dose escalation to MTD may be waived in Part 2. Dose escalation decisions will be made based on clinical safety and (when available) PK data (maximum or peak concentration [C_{max}] and area under the curve [AUC]) after review by the CRC, consisting of all Investigators and the Zenith Medical Monitor. If a DLT is observed in 1 of 3 patients in a cohort and confirmed by the CRC, 3 additional patients will be enrolled into that cohort. If 1 of 6 patients in a cohort experiences a DLT, then dose escalation may continue in the next cohort or the MTD of the combination can be declared. If ≥ 2 of 3 – 6 patients experience DLTs within a cohort, then the MTD will be considered to have been exceeded and further dose escalation will cease. In this case, if fewer than 6 patients have been enrolled at the previous dose level, that cohort will be expanded to 6 patients to confirm the MTD. Should the MTD of the combination be exceeded at Dose Level 1, a cohort may be explored with a reduced dose of ZEN003694 or enzalutamide at the discretion of the CRC. Cohort management is summarized below.

Number of Patients with Dose-limiting Toxicity	Action
1 of 1	Add 5 more patients
0 of 3	Proceed to next dose level
1 of 3	Add 3 more patients
1 of 6	Proceed to next dose level
≥ 2 of 3 or ≥ 2 of 6	Add 3 more patients in the next lower dose level if only 3 patients were treated in the next lower dose. If 6 patients were treated at the next lower dose level and no more than one patient had DLT, then the next lower dose is the MTD.

Part 1: Enrollment in Part 1 of the study with ZEN003694 in combination with enzalutamide will commence with 36 mg as the starting dose for ZEN003694 and 160 mg dose of enzalutamide (or at a lower stable dose for patients in DE-A or DC-A). The dose of enzalutamide will be held constant throughout Cycle 1 of Dose Escalation. After Cycle 1, enzalutamide toxicity may be managed per the XTANDI® Package Insert. Dose escalation will proceed per the schema below unless intervening toxicity is observed.

Dose Level	ZEN003694 (mg)	Fold Increase from Prior Dose Level
1	36	--
2	48	1.33
3	60	1.25
4	72	1.20
5	96	1.33
Additional levels may be explored at the discretion of the CRC		

Part 2: Enrollment in Part 2 of the study with ZEN003694 in combination with abiraterone will commence with 72 mg as the starting dose for ZEN003694 and 1000 mg dose of abiraterone once daily. The dose of abiraterone 1000 mg will be held constant throughout Cycle 1 of Dose Escalation. After Cycle 1, abiraterone toxicity may be managed per the ZYTIGA® Package Insert. Dose escalation/de-escalation will proceed per the schema below unless intervening toxicity is observed.

Dose Level	ZEN003694 (mg) *	Fold Increase from Prior Dose Level
-1	48	0.67
1	72	--
2	96	1.33
* Dose de-escalation from 72 mg is allowed by cohort. Additional dose levels may be explored based on safety and at the discretion of the CRC, with the proviso that dose escalation to MTD may be waived in Part 2.		

Part 1 and Part 2: Dose escalation increments between cohorts will be determined by the CRC based on safety and available PK data (e.g., C_{max} and AUC) based on the following schema:

- Dose escalation up to 2-fold is allowed in Dose Level 2 and 3 unless one drug-related Grade 2 event is observed in Dose Level 1 and 2, respectively
- Subsequent dose escalation up to 1.5-fold is allowed until a DLT is observed
- Subsequent dose escalation up to 1.33-fold is allowed until MTD is established, or, in Part 2, if MTD is waived and RP2D is declared

All dose escalations will be guided by the available PK data (e.g., C_{max} and AUC) from both **ZEN003694-001** and this study, ZEN003694-002, with respect to the combined AUC_{0-24} of ZEN003694 and its active metabolite ZEN003791. [redacted]

Intermediate doses and/or alternative dosing schedules may be evaluated to best determine the MTD and/or RP2D of ZEN003694 in combination with enzalutamide (Part 1) and abiraterone (Part 2) based on evaluation of clinical safety and available PK data (e.g., C_{max} and AUC) and upon agreement of the CRC members. No intra-patient dose escalation is allowed during the first three cycles of therapy. If a patient has not experienced any Grade 2 or higher drug-related AEs after three cycles, dose escalation up to the highest dose currently declared tolerable by the CRC will be allowed and further intra-patient dose escalation(s) will be determined on a cycle-by-cycle basis at the discretion of the Investigator and with approval from the CRC.

Teleconferences with members of the CRC will be held during the dose escalation phase to discuss any suspected DLTs that have occurred in patients within each cohort. The frequency of the teleconference calls will be determined by the rate of enrollment, data review, frequency of DLT notifications, discussions with investigational sites and other factors. Approximately one week after the last patient in a dose cohort completes Cycle 1 and prior to escalating to the next dose level (or de-escalating), the CRC will review toxicities and available PK (e.g., C_{max} and AUC) from the current cohort of the study during a teleconference.

Definition of Dose-limiting Toxicity

Determination of DLT will be made during the first 28 days of treatment (i.e., Cycle 1) in the dose escalation phase. Toxicity will be graded and recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03. A DLT is defined as a clinically significant AE or laboratory abnormality that is considered possibly, probably or definitely related to ZEN003694 and which meets any of the following criteria:

- Grade 3 or greater non-hematologic clinical toxicity with the exception of Grade 3 nausea or Grade 3/4 vomiting and diarrhea persisting less than 72 hours in the absence of maximal medical therapy
- Grade 4 neutropenia lasting more than 5 days
- Grade 3 or greater febrile neutropenia (temperature ≥ 38.5ºC)
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with clinically significant bleeding, or any requirement for platelet transfusion
- Any other Grade 3 or 4 laboratory abnormality that requires hospitalization
- An ALT > 3x ULN with concomitant total bilirubin > 2x ULN
- Any ZEN003694-related toxicity that results in more than 25% of missed doses during Cycle 1 of treatment
- In the situation where toxicity requires withholding ZEN003694 following the receipt of at least 75% of scheduled dosing during Cycle 1: Failure to begin Cycle 2 within 1 week of the scheduled start date due to ongoing toxicity.

All patients experiencing a DLT must discontinue dosing with ZEN003694; patients must complete the Safety Follow-up visit prior to discontinuation from the study.

Determination of evaluability will be made during the first 28 days of ZEN003694 treatment (i.e., Cycle 1) in the dose escalation phase. Patients meeting one or more of the following will be considered unevaluable and will be replaced:

- Patients who miss more than 25% of ZEN003694 and/or enzalutamide or abiraterone doses or fail to begin Cycle 2 within 1 week of the scheduled start date for reasons other than ZEN003694-related toxicity
- Patients who require enzalutamide or abiraterone dose hold or modification in Cycle 1, including during the 14-day Lead-in period for reasons other than ZEN003694-related toxicity.
- **Part 1 only:** If a patient is unable to tolerate enzalutamide for any reason at dose of 160 mg during the 14 day Lead-in prior to first dose of ZEN003694, then the patient should not receive ZEN003694, and be withdrawn from the study and replaced.
- **Part 2 only:** If a patient is unable to tolerate for any reason abiraterone at dose of 1000 mg once daily during the 14 day Lead-in prior to first dose of ZEN003694, then the patient should not receive ZEN003694, and be withdrawn from the study and replaced

Definition of the Maximum Tolerated Dose

The MTD is defined as the highest dose level of ZEN003694 in combination with enzalutamide (Part 1) or abiraterone (Part 2; if MTD is determined) at which no more than 1 of 6 patients experiences a DLT during the first cycle of therapy. MTD may be declared independently for any given dosing regimen, i.e., the respective MTDs for once daily dosing, twice daily dosing, and any alternative dosing regimen(s) need not be at the same dose.

Definition of the Recommended Phase 2 Dose

The RP2D is defined as the dose level of ZEN003694 in combination with enzalutamide (Part 1) or abiraterone (Part 2) recommended for further clinical study. In Part 1 of this study, the RP2D may be the same as the MTD or modified from the MTD based on assessment of overall exposure, safety experience in Cycle 2 and beyond, PD and clinical benefit data. In Part 2 of this study, the MTD establishment may be waived and the RP2D will then be based on assessment of overall exposure, safety experience in Cycle 2 and beyond, PD and clinical benefit data; alternatively, it may be based on the MTD established. The RP2D of ZEN003694 in combination with enzalutamide (Part 1) or abiraterone (Part 2) will be determined in the dose confirmation phase of the study. RP2D may be declared independently for any given Part of the study or dosing regimen, i.e., the respective RP2Ds for once daily dosing, twice daily dosing, and any alternative dosing regimen(s) need not be at the same dose.

Dose Confirmation

Part 1 only: Once the MTD of ZEN003694 in combination with enzalutamide has been determined in the dose escalation portion of Part 1 of the study, up to 20 patients who meet the inclusion/exclusion criteria for Cohort DC-A and up to 20 patients who meet the inclusion/exclusion criteria for Cohort DC-B of the dose confirmation phase will be enrolled for further evaluation of safety, PK, PD and preliminary clinical activity.

Enzalutamide-naive and apalutamide-naïve patients in Cohort DC-B will be administered enzalutamide (160 mg) orally once daily for 14 days prior to the initiation of the combination therapy (Lead-in) to reach enzalutamide C_{ss} during Cycle 1. After the Lead-in, ZEN003694 will be administered orally in combination with daily enzalutamide for 28-day cycles. Patients in Cohort DC-A who are currently receiving a stable dose of enzalutamide (Sub-arm A1) will continue to receive enzalutamide and will not participate in the Lead-in. Patients in Cohort DC-A who are not currently receiving enzalutamide or apalutamide or are currently taking apalutamide (Sub-arm A2) will be administered enzalutamide orally once daily for 14 days prior to the initiation of the combination therapy (Lead-in) to reach enzalutamide C_{ss}. After the Lead-in, ZEN003694 will be administered orally in combination with daily enzalutamide for 28-day cycles.

Part 2 only: Once the CRC has determined a recommended phase 2 dose of ZEN003694 in combination with abiraterone in the dose escalation portion of Part 2 of the study, up to 20 patients who meet the inclusion/exclusion criteria for Cohort DC-C and up to 20 patients who meet the inclusion/exclusion criteria for Cohort DC-D of the dose confirmation phase will be enrolled for further evaluation of safety, PK, PD and preliminary clinical activity.

Abiraterone-naïve patients in Cohort DC-D will be administered abiraterone (1000 mg once daily) orally for 14 days prior to the initiation of the combination therapy (Lead-in) to reach abiraterone C_{ss} during Cycle 1. After the Lead-in, ZEN003694 will be administered orally in combination with daily abiraterone for 28-day cycles. Patients in Cohort DC-C who are currently receiving a stable dose of abiraterone (Sub-arm C1) will continue to receive abiraterone when enrolled in the dose confirmation phase of the study and will not participate in the Lead-in. Patients in Cohort DC-C who are not currently receiving abiratertone (Sub-Arm C2) will be administered abiraterone orally

once daily for 14 days prior to the initiation of the combination therapy (Lead-in) to reach abiraterone C_{ss}. After the Lead-in, ZEN003694 will be administered orally in combination with daily abiraterone for 28-day cycles.

Part 1 and Part 2: When the 6th patient in each cohort in the dose confirmation phase has completed one cycle of therapy, or earlier if clinically indicated, the CRC will review the safety data. If ≥ 2 patients have experienced drug-related SAEs or DLT-equivalent events, the CRC may recommend a modification in the dose or regimen of ZEN003694 in combination with enzalutamide for the dose confirmation phase.

NUMBER OF SITES:

Up to 10 sites in the United States may participate in this study.

NUMBER OF PATIENTS:

Part 1: Up to 80 evaluable patients will be enrolled in the study; approximately 40 patients will be enrolled in the dose escalation phase and up to 40 patients will be enrolled in the dose confirmation phase.

Part 2: Up to 55 evaluable patients will be enrolled in the study; approximately 15 patients will be enrolled in the dose escalation phase and up to 40 patients will be enrolled in the dose confirmation phase.

ESTIMATED STUDY DURATION:

The study duration including the enrollment period and follow-up for both the dose escalation and dose confirmation phases is approximately 36 months for Part 1 and 24 months for Part 2, depending upon total enrollment.

ELIGIBILITY CRITERIA:

Part 1:, ZEN003694 in combination with enzalutamide

Part 1 Inclusion Criteria

Patients must meet the following inclusion criteria to be eligible for the study.

Part 1 All Patients

1. Males age ≥ 18 years
2. Metastatic, castrate resistant, histologically confirmed prostate cancer; surgically castrated or continuous medical castration for ≥ 8 weeks prior to screening
3. Serum testosterone < 50 ng/dL determined within 4 weeks of first administration of study drug
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
5. Adequate laboratory parameters at Screening including:
    a. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
    b. Platelet count ≥ 100,000/mm^3

c. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤ 2.0 x ULN (≤ 5 x ULN if liver metastases are present)

d. Total bilirubin ≤ 1.25 x ULN

e. Serum creatinine ≤ 1.5 x ULN or calculated (Cockcroft-Gault formula) or measured creatinine clearance ≥ 60 mL/min

f. Prothrombin time (PT), international normalized ratio (INR) and partial thromboplastin time (PTT) < 1.5 x ULN

6. Use of corticosteroids is allowed up to a daily dose of 10 mg prednisone or equivalent provided that the dose has been stable for at least 2 weeks prior to first administration of study drug and will remain stable during study drug and enzalutamide dosing

7. Patients must be surgically sterile or must agree to use physician-approved contraception during the study and for 30 days following the last study drug administration

8. Ability to swallow capsules and comply with study procedures

9. Ability to understand and willingness to sign informed consent form prior to initiation of any study procedures

Part 1 Dose Escalation only

10. Cohort DE-A: Prior progression on enzalutamide or apalutamide at any time by PCWG2 criteria and is or will be receiving a stable dose of enzalutamide (defined as a dose that has not changed for at least 2 weeks prior to Cycle 1 Day 1 and is not expected to change on study). Patients may or may not have experienced prior progression on abiraterone.

11. Cohort DE-B: Enzalutamide-naïve and apalutamide-naïve patients following prior progression on abiraterone by PCWG2 criteria.

Part 1 Dose Confirmation only

12. Cohort DC-A: Prior progression on enzalutamide or apalutamide at any time by PCWG2 criteria and is or will be receiving a stable dose of enzalutamide (defined as a dose that has not changed for at least 2 weeks prior to Cycle 1 Day 1 and is not expected to change on study). Patients may or may not have experienced prior progression on abiraterone.

13. Cohort DC-B: Enzalutamide-naïve and apalutamide-naïve patients following prior progression on abiraterone by PCWG2 criteria.

Part 1 Exclusion Criteria

Patients who meet any of the following exclusion criteria will not be eligible to participate in the study.

1. Any history of brain metastases or prior seizure or conditions predisposing to seizure activity

2. Have previously received an investigational BET inhibitor (including previous participation in this study or Study **ZEN003694-001**)

3. Have received prior systemic anti-cancer therapy (including abiraterone) or investigational therapy within 2 weeks or five half-lives, whichever is shorter, prior to the first administration of study drug
4. Failure to recover to Grade 1 or lower toxicity related to prior systemic therapy (excluding alopecia and neuropathy) prior to study entry
5. Radiation therapy within 2 weeks of the first administration of study drug
6. Treatment with a bone-targeted radionuclide within 6 weeks of first administration of study drug (enzalutamide in DE-B and DC-B or ZEN003694 in DE-A and DC-A)
7. Have received prior chemotherapy in the metastatic castration-resistant setting (prior chemotherapy in the hormone-sensitive setting is allowed provided last dose was at least 6 months prior to study entry)
8. Have received prior investigational anti-androgen therapy
9. Currently receiving medications known to be strong inhibitors of cytochrome (CYP)2C8, strong inducers (except enzalutamide or apalutamide) or inhibitors of CYP3A4 and substrates of CYP1A2, CYP3A4, CYP2C9 and CYP2C19 with a narrow therapeutic window. Strong inducers, inhibitors and substrates must be discontinued at least 7 days prior to the first administration of study drug.
10. Not a candidate for enzalutamide treatment, in the opinion of the Investigator
11. Left ventricular ejection fraction less than the lower of 50% or the lower limit of institution's normal range
12. QTcF interval > 450 msec
13. Known impaired cardiac function or clinically significant cardiac disease such as uncontrolled supraventricular arrhythmia, ventricular arrhythmia requiring therapy, or congestive heart failure (New York Heart Association functional class III or IV)
14. Myocardial infarction or unstable angina within 6 months prior to the first administration of study drug
15. Other clinically significant co-morbidities, such as uncontrolled pulmonary disease, active central nervous system disease, active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy, or any other condition that could compromise safety or the patient's participation in the study
16. Other known active cancer requiring therapy at time of study entry
17. Historically positive (screening tests not required) for human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) or with active infections. HBV positivity defined by positive hepatitis B surface antigen (HBsAg). HCV positivity defined as positive HCV viral load
18. Major surgery other than diagnostic surgery, dental surgery or stenting within 4 weeks prior to the first administration of study drug
19. History of congenital or other deficiency in platelet function, any known inherent or

acquired coagulopathy, or therapeutic anticoagulation with warfarin or apixaban (low-dose warfarin for port patency or prophylactic anti-platelet agents are allowed)

20. Concurrent participation in another clinical investigational treatment trial

21. Any other reason that in the opinion of the Investigator would prevent the patient from completing participation or following the study schedule

Part 2 Only, ZEN003694 in combination with abiraterone:

Part 2 Inclusion Criteria

Patients must meet the following inclusion criteria to be eligible for the study.

Part 2 All Patients

1. Males age ≥ 18 years

2. Metastatic, castrate resistant, histologically confirmed prostate cancer; surgically castrated or continuous medical castration for ≥ 8 weeks prior to screening

3. Serum testosterone < 50 ng/dL determined within 4 weeks of first administration of study drug

4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

5. Adequate laboratory parameters at Screening including:

    a. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L

    b. Platelet count ≥ 100,000/mm^3

    c. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤ 2.0 x ULN (≤ 5 x ULN if liver metastases are present)

    d. Total bilirubin ≤ 1.25 x ULN

    e. Serum creatinine ≤ 1.5 x ULN or calculated (Cockcroft-Gault formula) or measured creatinine clearance ≥ 60 mL/min

    f. Prothrombin time (PT), international normalized ratio (INR) and partial thromboplastin time (PTT) < 1.5 x ULN

6. Use of corticosteroids is allowed up to a daily dose of 10 mg prednisone or equivalent provided that the dose has been stable for at least 2 weeks prior to first administration of study drug and will remain stable during study drug and abiraterone dosing

7. Patients must be surgically sterile or must agree to use physician-approved contraception during the study and for 30 days following the last study drug administration

8. Ability to swallow capsules and comply with study procedures

9. Ability to understand and willingness to sign informed consent form prior to initiation of any study procedures

Part 2 Dose Escalation only

10. Cohort DE-C: Prior progression on abiraterone at any time by PCWG2 criteria and is or will be receiving a stable dose of abiraterone (defined as a dose that has not changed for at least 2 weeks prior to Cycle 1 Day 1 and is not expected to change on study). Patients may or may not have experienced prior progression on enzalutamide or apalutamide.

11. Cohort DE-D: Abiraterone-naïve patients following prior progression on enzalutamide or apalutamide by PCWG2 criteria.

Part 2 Dose Confirmation only

12. Cohort DC-C: Prior progression on abiraterone at any time by PCWG2 criteria and is or will be receiving a stable dose of abiraterone (defined as a dose that has not changed for at least 2 weeks prior to Cycle 1 Day 1 and is not expected to change on study). Patients may or may not have experienced prior progression on enzalutamide or apalutamide.

13. Cohort DC-D: Abiraterone-naïve patients following prior progression on enzalutamide or apalutamide by PCWG2 criteria.

Part 2 Exclusion Criteria

Patients who meet any of the following exclusion criteria will not be eligible to participate in the study.

1. Have previously received an investigational BET inhibitor (including previous participation in this study or Study **ZEN003694-001**)

2. Have received prior systemic anti-cancer therapy or investigational therapy within 2 weeks or five half-lives, whichever is shorter, prior to the first administration of study drug. (Patients progressing on enzalutamide or apalutamide require a 2 week wash-out prior to start of abiraterone Cycle 1 Lead-in where applicable)

3. Failure to recover to Grade 1 or lower toxicity related to prior systemic therapy (excluding alopecia and neuropathy) prior to study entry

4. Radiation therapy within 2 weeks of the first administration of study drug

5. Treatment with a bone-targeted radionuclide within 6 weeks of first administration of study drug (abiraterone in DE-D and DC-D or ZEN003694 in DE-C and DC-C)

6. Have received prior chemotherapy in the metastatic castration-resistant setting (prior chemotherapy in the hormone-sensitive setting is allowed provided last dose was at least 6 months prior to study entry)

7. Have received prior investigational anti-androgen therapy

8. Currently receiving medications known to be substrates of CYP1A2 or CYP2D6 with a narrow therapeutic window. Major substrates must be discontinued at least 7 days prior to the first administration of study drug.

9. Not a candidate for abiraterone treatment, in the opinion of the Investigator

10. Left ventricular ejection fraction less than the lower of 50% or the lower limit of

institution's normal range

11. QTcF interval > 450 msec
12. Known impaired cardiac function or clinically significant cardiac disease such as uncontrolled supraventricular arrhythmia, ventricular arrhythmia requiring therapy, or congestive heart failure (New York Heart Association functional class III or IV)
13. Myocardial infarction or unstable angina within 6 months prior to the first administration of study drug
14. Other clinically significant co-morbidities, such as uncontrolled pulmonary disease, active central nervous system disease, active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy, or any other condition that could compromise safety or the patient's participation in the study
15. Other known active cancer requiring therapy at time of study entry
16. Historically positive (screening tests not required) for human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) or with active infections. HBV positivity defined by positive hepatitis B surface antigen (HBsAg). HCV positivity defined as positive HCV viral load
17. Major surgery other than diagnostic surgery, dental surgery or stenting within 4 weeks prior to the first administration of study drug
18. History of congenital or other deficiency in platelet function, any known inherent or acquired coagulopathy, or therapeutic anticoagulation with warfarin or apixaban (low-dose warfarin for port patency or prophylactic anti-platelet agents are allowed)
19. Concurrent participation in another clinical investigational treatment trial
20. Any other reason that in the opinion of the Investigator would prevent the patient from completing participation or following the study schedule

DOSE, REGIMEN AND ROUTE OF ADMINISTRATION:

ZEN003694

ZEN003694 is a novel, potent BET bromodomain inhibitor currently under clinical investigation. ZEN003694 will be supplied in capsules of two different dosage strengths: 12 mg and 48 mg.

Part 1: The starting dose for this study is 36 mg daily. Dosing in initial cohorts will commence with ZEN003694 administered once daily ZEN003694 in combination with enzalutamide (160 mg or at a lower stable dose for patients in DE-A or DC-A). Alternative dosing regimens (i.e., twice daily dosing, on/off schedules) may be explored in separate dose cohorts based on CRC safety review and approval.

Part 2: The starting dose for this study is 72 mg daily. Dosing in initial cohorts will commence with ZEN003694 administered once daily ZEN003694 in combination with abiraterone (1000 mg once daily) orally. Alternative dosing regimens (i.e., twice daily dosing, on/off schedules) may be explored in separate dose cohorts based on CRC safety review and approval.

Both Part 1 and Part 2: ZEN003694 will be administered orally in 28-day cycles and should be ingested with a full (8-ounce) glass of water at least 1 hour before eating or 2 hours after eating (fasting).

Part 1: Enzalutamide

Enzalutamide is an androgen receptor inhibitor indicated for the treatment of patients with mCRPC. Enzalutamide 160 mg (four 40 mg capsules) will be administered orally once daily according to the XTANDI® Package Insert without food in 28-day cycles for all enzalutamide-naïve patients (DE-B and DC-B cohorts). For patients in DE-A and DC-A cohorts, enzalutamide will be administered at the dose level previously determined to be stable and that has not changed for at least two weeks prior to starting Cycle 1 Day 1 combination study treatment or restarting enzalutamide treatment in the Lead-in phase. In Dose Escalation, the dose of enzalutamide will be held constant throughout Cycle 1 of the study. After Cycle 1, the dose of enzalutamide may be modified for toxicity per the XTANDI® Package Insert.

Patients may continue receiving ZEN003694 in combination with enzalutamide until disease progression by PCWG2 criteria, unacceptable toxicity, requirement for non-protocol therapy or patient withdrawal from study. Patients with PSA-only progression may remain on study until clinical and/or radiographic evidence of progression by PCWG2 criteria.

Part 2: Abiraterone

Abiraterone is an androgen synthesis inhibitor indicated for the treatment of patients with mCRPC. Abiraterone 1000 mg (four 250 mg capsules) will be administered orally once daily according to the ZYTIGA® Package Insert without food in 28-day cycles. In Dose Escalation, the dose of abiraterone will be held constant at 1000 mg throughout Cycle 1 of the study. After Cycle 1, the dose of abiraterone may be modified for toxicity per the ZYTIGA® Package Insert.

Patients may continue receiving ZEN003694 in combination with abiraterone until disease progression by PCWG2 criteria, unacceptable toxicity, requirement for non-protocol therapy or patient withdrawal from study. Patients with PSA-only progression may remain on study until clinical and/or radiographic evidence of progression by PCWG2 criteria.

STUDY ASSESSMENTS:

Safety

Safety will be assessed by periodic physical examinations, weight, ECOG performance status, vital signs, clinical laboratory assessments (hematology, serum chemistries, serum troponin, coagulation tests and urinalysis), 12-lead electrocardiogram (ECG) and monitoring of AEs (see Schedule of Events).

Pharmacokinetics

Part 1: Plasma samples will be collected to assess the PK properties of ZEN003694 and the metabolite ZEN003791, and enzalutamide and the metabolite des-methyl enzalutamide. Urine samples may also be collected at the direction of Zenith in the Dose Confirmation phase to assess ZEN003694 and its metabolites, including ZEN003791. Plasma and urine concentrations of ZEN003694, the metabolite ZEN003791, enzalutamide and des-methyl enzalutamide will be determined by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) bioanalytical method. Samples will be collected as indicated in the Schedule of Events.

Part 2: Plasma samples will be collected to assess the PK properties of ZEN003694 and the metabolite ZEN003791, and abiraterone. Plasma concentrations of ZEN003694, the metabolite ZEN003791, and abiraterone will be determined by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) bioanalytical method. Samples will be collected as indicated in the Schedule of Events.

Pharmacodynamics

Blood samples will be drawn for analyses of BET inhibitor gene expression profile, cell-free DNA and circulating tumor DNA, CTCs and exploratory biomarkers (dose confirmation only) as indicated in the Schedule of Events. Blood samples for analyses of immuno-oncology biomarkers will also be drawn at selected clinical sites. Tumor tissue will be obtained for histological and immunohistochemical analyses, expression of V-Myc avian myelocytomatosis viral oncogene homolog (MYC), glucocorticoid receptor (GR) and androgen receptor (AR), and RNA sequencing (and DNA sequencing if adequate tumor tissue is available) analysis to identify somatic mutations, alternative splicing, fusions and alterations in gene expression. Tumor tissue will be obtained as indicated in the Schedule of Events.

Response

Whole body radionuclide imaging (Tech-99) and cross-sectional imaging of the chest/abdomen/pelvis should be performed in accordance with institutional standards. Use of intravenous contrast is required unless contraindicated. Magnetic resonance imaging (MRI) may be substituted for computed tomography (CT) per the Investigator's discretion. Disease status should be assessed using the PCWG2 criteria as indicated in the Schedule of Events.

Blood samples will be drawn to measure PSA levels as indicated in the Schedule of Events.

Whole blood samples will be drawn for enumeration of CTCs as indicated in the Schedule of Events.

STATISTICAL METHODS:

The primary statistical analysis of the data will be descriptive in nature. For continuous variables this means calculation of the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by patient counts and related percentages. For ordinal-scaled variables, a combination of the above may be employed as appropriate: frequency and percentage of observations within a category and means and standard deviations of the scores of the categories. For categorical and ordinal variables, percentages will be calculated based on non-missing data.

Based on the characteristics of the study design and lack of a concurrent control arm, formal testing of treatment effects (i.e., inferential statistics) will not be performed. However, some measures will be summarized by both point estimates and the associated 95% confidence intervals.

Sample Size Determination

A conventional algorithm (3+3 patients per dose level) will be used to identify the MTD, escalating on 0 of 3 or 1 of 6 DLTs, and de-escalating if 2 DLTs are encountered. The MTD will be the highest dose level at which 0 of 3 or 1 of 6 patients experience a DLT, with the next higher dose having at least 2 of 3 or 2 of 6 patients experiencing a DLT. With this design, there is a 71% chance of escalation if the true but unknown rate of DLT is 20%, and less than 50% chance of escalation if the true but unknown rate of DLT is higher than 30%.

Part 1: Approximately 40 patients may be enrolled in the dose escalation phase of the study. Up to 40 patients in the dose confirmation phase may be enrolled at the MTD or RP2D. The sample size is sufficient to support preliminary safety and pharmacologic assessments.

Part 2: Approximately 15 patients may be enrolled in the dose escalation phase of the study. Up to 40 patients in the dose confirmation phase may be enrolled at the MTD or RP2D. The sample size is sufficient to support preliminary safety and pharmacologic assessments.

Analysis Populations

The following populations will be analyzed by Part:

Safety population: Patients who receive at least one dose of ZEN003694.

DLT population: Patients who experience a DLT as defined by this protocol. Patients who experience a DLT within the first cycle of treatment and drop out of the study will be considered evaluable for DLT and will not be replaced.

- Part 1 only: No dose modification of enzalutamide (160 mg) is permitted during Cycle 1, including the 14-day Lead-in period; patients requiring dose modification during Cycle 1 must discontinue the study and will be replaced. Patients, who for reasons other than a DLT, discontinue the study prior to completion of the first cycle will be considered unevaluable and will be replaced.
- Part 2 only: No dose modification of abiraterone (1000 mg) is permitted during Cycle 1, including the 14-day Lead-in period; patients requiring dose modification during Cycle 1 must discontinue the study and will be replaced. Patients, who for reasons other than a DLT, discontinue the study prior to completion of the first cycle will be considered unevaluable and will be replaced.

Statistical Analyses

Prior to the analysis of the final study data, a detailed statistical analysis plan (SAP) will be written. Detailed information regarding analysis datasets, summarization of the data and analyses will be provided in the SAP.

Table 1: PART 1 ONLY: ZEN003694 + Enzalutamide

Schedule of Events – Dose Escalation (DE) and Dose Confirmation (DC)

	Screening (Within 28 Days of C1D-14 for DE-B and DC-B or C1D1 for DE-A and DC-A)	Cycle 1 (Days -14 through -1)	Cycle 1 (Days 1 – 28)	Cycle 2 (Days 1 – 28)	Cycle 3 Onward (Days 1 – 28)	Unscheduled Visit [v]	End of Treatment [w]	Safety Follow-up (30 Days after End of Treatment) [x]
Medical, Surgical, Malignancy History, Prior Cancer Treatments, Demographics	X							
Informed Consent	X							
Physical Examination, Weight, Height, ECOG Performance Status, Vital Signs [a]	X		Days 1, 8, 15, 22	Days 1, 15	Days 1	X	X	X
Hematology [b]	X	DE-B and DC-B: *Day -14 DE-A and DC-A Sub-arm A2^	Days 1*, 8, 15, 22	Days 1, 8, 15, 22	Days 1, 15	X	X	X
Coagulation Tests [c]	X	DE-B and DC-B: *Day -14 DE-A and DC-A Sub-arm A2^	Days 1*, 15	Day 1	Day 1	X		
Serum Chemistries [d]	X	DE-B and DC-B: *Day -14 DE-A and DC-A Sub-arm A2^	Days 1*, 8, 15, 22	Days 1, 8, 15, 22	Days 1, 15	X	X	X
Troponin [e]			Days 1, 15	Day 1	Day 1		X	
Serum Prostate-specific Antigen	X	DE-B and DC-B: *Day -14 DE-A and DC-A Sub-arm A2^	Day 1*	Day 1	Day 1		X	X
Urinalysis [f]	X	DE-B and DC-B: *Day -14 DE-A and DC-A Sub-arm A2^	Day 1*	Day 1	Day 1	X	X	X
Serum Testosterone	X		Day 1	Day 1	Day 1		X	X

	Screening (Within 28 Days of C1D-14 for DE-B and DC-B or C1D1 for DE-A and DC-A)	Cycle 1 (Days -14 through -1)	Cycle 1 (Days 1 – 28)	Cycle 2 (Days 1 – 28)	Cycle 3 Onward (Days 1 – 28)	Unscheduled Visit [v]	End of Treatment [w]	Safety Follow-up (30 Days after End of Treatment)[x]
Echocardiogram or Multigated Acquisition Scan [g]	X							
Triplicate 12-Lead Electrocardiogram [h]	X		Days 1, 15	Day 1	Day 1 [h]	X		
Ophthalmology Assessments[i]	X [i]			Day 1	Cycle 6 Day 1 onward [i]	X [i]	X	X [i]
Qualitative Exploration of Visual Symptoms [i]	X	X	Days 1, 8, 15, 22	Days 1, 15	Days 1		X	X
Fresh Tumor and Archival Tumor Tissue Collection (Optional for DE, Mandatory for DC for Patients with Accessible Tumors)	X [j]				X [k]		X [l]	
Pharmacokinetics [m]			Days 1, 2, 15	Day 1				
BET Inhibitor Gene Expression Profile [n]			Days 1, 2					
Circulating Tumor Cells (CTCs) for Pharmacodynamic/Correlative Evaluation [o]		DE-B and DC-B: Day -14 DE-A and DC-A Sub-arm A2^	Day 1		Day 1 [o]		X	
CTCs for Enumeration/Response Analysis [p]		DE-B and DC-B: Day -14 DE-A and DC-A Sub-arm A2^	Day 1		Day 1 [p]		X	
Exploratory PD Biomarkers (DC Only) [q]		DC-B: Day -14 DC-A Sub-arm A2^	Day 1	Day 1			X	
Exploratory Immuno-Oncology Biomarkers [r] (DE Only, select sites only)	X[r]		Days 1 [r], 8, 22					
ZEN003694 Administration [s]			Days 1 through 28 of each cycle					
Enzalutamide Administration [t]		DE-B and DC-B: Days -14 through -1	Days 1 through 28 of each cycle					

	Screening (Within 28 Days of C1D-14 for DE-B and DC-B or C1D1 for DE-A and DC-A)	Cycle 1 (Days -14 through -1)	Cycle 1 (Days 1 – 28)	Cycle 2 (Days 1 – 28)	Cycle 3 Onward (Days 1 – 28)	Unscheduled Visit [v]	End of Treatment [w]	Safety Follow-up (30 Days after End of Treatment)[x]
		DE-A and DC-A Sub-arm A2^						
Adverse Events		DE-B and DC-B: Day -14 DE-A and DC-A Sub-arm A2^	Days 1, 8, 15, 22	Days 1, 15	Day 1	X	X	X
Prior/Concomitant Medications	X	DE-B and DC-B: Day -14 DE-A and DC-A Sub-arm A2^	Days 1, 8, 15, 22	Days 1, 15	Day 1	X	X	X
Tumor Assessment [u]	X				X [u]	X	X	
Exploratory BET Inhibitor Blood Signature (DC only) [y]			Day 1	Day 1	X [y]		X	
Urinalysis for Renal Clearance (DC Only) [z]			Day 15					
Exploratory cfDNA and ctDNA[aa]		DE-B and DC-B Day -14 DE-A and DC-A Sub-arm A2^	Day 1		Day 1		X	

Cycle 1 Day -14 Enzalutamide Lead-in should begin -14 days ± 1 day from Cycle 1 Day 1. All other scheduled clinic attendance should occur within ± 3 days of the specified dates at all visits unless otherwise specified. Imaging for tumor assessments may be scheduled up to 7 days prior to the scheduled clinic visit day.

* For patients requiring enzalutamide Lead-in, perform laboratory tests at Cycle 1 Day -14 only if Screening visit tests were performed more than 7 days prior to the Cycle 1 Day -14 visit. For patients that do not require enzalutamide Lead-in, perform laboratory tests at Cycle 1 Day 1 only if Screening visit tests were performed more than 7 days prior to the Cycle 1 Day 1 visit.

^ Only for patients in DE-A or DC-A who are not currently taking enzalutamide or are currently taking apalutamide, enzalutamide is to be (re)started with a 14 day Lead-in and Visit C1D-14 shall be conducted for applicable patients (DE-A and DC-A Sub-arm A2)

All assessments and tests/samples should be obtained pre-dose unless specified otherwise, and are to be performed even if dosing is not required (i.e., due to an on/off schedule) on the specified study visit day. Note: The visits in Cycle 2, on Days 8 and 22 and in Cycle 3 onward, on Day 15, will only include blood draws for safety laboratory testing and may be drawn after the patient has taken his dose (if dosing is required on that day).

Footnotes:

[a] Complete physical examination to be performed at the Screening visit and a symptom-directed physical examination thereafter. Height to be measured at the Screening Visit only. Vital signs: body temperature, blood pressure and heart rate.

[b] Hematology: complete blood count (CBC) with differential and absolute neutrophil count (ANC). Day 15 hematology can be waived at Investigator discretion starting in Cycle 6 onward as long as platelets are stable and there are no other laboratory concerns in the opinion of the Investigator.

[c] Coagulation tests: prothrombin time (PT) or international normalized ratio (INR) and partial thromboplastin time (PTT)

[d] Serum chemistry: albumin, alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase, amylase, bicarbonate, total bilirubin, blood urea nitrogen (BUN), total calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), lipase, sodium, potassium, phosphorus and magnesium. Note: Serum testosterone will be collected at screening , Day 1 of each cycle, and at EOT and Safety Follow-up. Day 15 serum chemistries can be waived at Investigator discretion starting in Cycle 6 onward as long as platelets are stable and there are no other laboratory concerns in the opinion of the Investigator.

[e] Troponin: serum samples will be drawn for analyses of troponin T and/or I proteins, based on local laboratory procedure. For any individual patient, the same method will be used at each timepoint.

[f] Urinalysis: dipstick with micro-analysis if clinically indicated.

[g] Cardiac echocardiogram or multigated acquisition (MUGA) scan for left ventricular ejection fraction

[h] Triplicate 12-lead electrocardiogram (ECG) to be performed as follows for each Part. For DE, DC-A and DC-B: Cycle 1 Day 1: pre-dose and 1 hour (±15 min) post-ZEN003694 and enzalutamide doses; Cycle 1 Day 15: pre-dose and 1 hour (±15 min) post-ZEN003694 and enzalutamide doses; Cycle 2 Day 1: pre-ZEN003694 and enzalutamide doses; Cycle 3 Day 1 and every other cycle onward (C5D1, C7D1, etc.): pre-ZEN003694 and enzalutamide doses.

[i] Ophthalmology assessments will be performed at Screening, C2D1, C6D1 (and every sixth cycle onward) and at the End of Treatment (±7 days at each visit). Screening ophthalmology assessments are to be performed prior to C1D1 and after all entry criteria have been assessed and the subject is approved for enrollment in the study. If abnormalities are detected or there are visual disturbances noted at the End of Treatment, ophthalmology assessments are to be performed at the Safety Follow-Up visit. At any time during the study should a clinically meaningful change in visual symptoms occur, unscheduled assessments are to be performed. Ophthalmology assessments will include: Ophthalmic history, Snellen best corrected visual acuity (including refraction, if needed), color vision testing (using standard HRR pseudoisochromatic plates), pupillometry, confrontational visual field testing, intraocular pressure (using Goldmann tonometry or TonoPen tonometry), external eye and ocular motility exam and slit lamp biomicroscopy, indirect ophthalmoscopy, OCT optic nerve and macula tests, fundus photography, and other exams as clinically indicated. Completion of the Qualitative Exploration of Visual Symptoms form (provided by the Sponsor) is required at every clinic visit.

[j] Fresh tumor sample collections are optional and encouraged at Screening during the DE phase. Fresh tumor samples are mandatory at Screening during the DC phase for patients with accessible lesions. During each biopsy procedure, 2-4 tumor tissue cores (optimally 4 cores) should be obtained. For those patients in DE-A or DC-A who are not currently taking enzalutamide and require 14 day Lead-in, the screening fresh tumor biopsy can be collected from time of consent through Cycle 1 Day -1, preferably during the 14 day enzalutamide Lead-in. Archival tumor samples (initial diagnostic tissue or from prostatectomy or other resected tissue), if available and with the patient's consent, will be collected during the Screening period through the end of Cycle 2 or the End of Treatment, whichever occurs first.

[k] Fresh tumor sample collections at Cycle 3 Day 1 (± 15 days) during the DE phase are encouraged yet optional. Fresh tumor sample collections at Cycle 3 Day 1 (± 15 days) during the DC phase are mandatory if the tumor is accessible. During each biopsy procedure, 2-4 tumor tissue cores (optimally 4 cores) should be obtained.

[l] An optional biopsy will be taken at the time of disease progression by Prostate Cancer Working Group 2 (PCWG2) criteria for patients in DE or DC phases of the study. Whenever possible, this biopsy should be performed while the patient is still receiving ZEN003694 and enzalutamide, and 2 to 4 hours following administration of ZEN003694 and enzalutamide on the day of biopsy.

[m] Blood (plasma) for pharmacokinetic (PK) profile of ZEN003694 and enzalutamide and their active metabolites will be collected in **DE, DC-A and DC-B** as specified below:

- C1D1: pre-ZEN003964 and enzalutamide doses
- C1D1: 15 min (±5 min), 30 min (±5 min), 1 hour (±5 min), 2 hours (±10 min), 4 hours (±15 min), 6 hours (±15 min) and 8 hours (±30 min) post-ZEN003694 and enzalutamide doses
- C1D2: pre-ZEN003694 and enzalutamide doses
- C1D15: pre-ZEN003964 and enzalutamide doses
- C1D15: 15 min (±5 min), 30 min (±5 min), 1 hour (±5 min), 2 hours (±10 min), 4 hours (±15 min), 6 hours (±15 min) and 8 hours (±30 min) post-ZEN003694 and enzalutamide doses
- C2D1: pre-ZEN003964 and enzalutamide doses
- If enzalutamide dose is reduced in DE any time after Cycle 1 or in DC at any time, PK samples are to be collected 28 days ±7 days following dose modification: pre-ZEN003964 and enzalutamide doses, and 15 min (±5 min), 30 min (±5 min), 1 hour (±5 min), 2 hours (±10 min), 4 hours (±15 min), 6 hours (±15 min) and 8 hours (±30 min) post-ZEN003694 and enzalutamide doses

[n] Blood samples (whole blood) for BET inhibitor gene expression profile:

- C1D1: pre-ZEN003694 and enzalutamide doses
- C1D1: 2 hours (±15 min), 4 hours (±15 min), and 6 hour (±15 min) post-ZEN003694 and enzalutamide doses

- C1D2: pre-ZEN003694 and enzalutamide doses
- Unscheduled blood samples (whole blood) for BET inhibitor gene expression profile at pre-dose, 2 hours (±15 min), 4 hours (±15 min), and/or 6 hour (±15 min) post-ZEN003694 and enzalutamide doses may also be drawn at later time-points, upon direction by Zenith

[o] Blood samples (whole blood) for CTCs for PD/correlative evaluation:

- C1D-14: pre-enzalutamide dose (**for all patients requiring enzalutamide Lead-in)**
- C1D1: pre-ZEN003694 and enzalutamide doses
- C3D1: pre-ZEN003694 and enzalutamide doses
- Every third cycle D1 (C6D1, C9D1, etc.): pre-ZEN003694 and enzalutamide doses
- At disease progression and at the time of PSA or radiographic response

[p] Blood samples (whole blood) for CTCs for enumeration/response analysis:

- C1D-14: pre-enzalutamide dose (**for all patients requiring enzalutamide Lead-in**)
- C1D1: pre-ZEN003694 and enzalutamide doses
- C3D1: pre-ZEN003694 and enzalutamide doses
- Every third cycle D1 (C6D1, C9D1, etc.): pre-ZEN003694 and enzalutamide doses
- At disease progression and at the time of PSA or radiographic response

[q] Blood samples (plasma) for exploratory PD assessments (**DC-A and DC-B**):

- C1D-14: pre-enzalutamide dose (**for all patients requiring enzalutamide Lead-in)**
- C1D1: pre-ZEN003694 and enzalutamide doses
- C2D1: pre-ZEN003694 and enzalutamide doses
- At study treatment discontinuation

[r] Blood samples (whole blood) for immuno-oncology biomarker assessments (**DE Only**, at selected clinical sites only)

- Screening (Prior to the first dose of enzalutamide for the Day -14 Lead-in for all patients requiring enzalutamide Lead-in. Prior to ZEN003694 dosing on C1D1 of DE-A or DC-A for patients who do not require enzalutamide Lead-in.)
- C1D1: For all patients requiring enzalutamide Lead-in, pre-ZEN003694 and pre-enzalutamide dosing
- C1D8: pre-ZEN003694 and pre-enzalutamide dosing
- C1D22: pre-ZEN003694 and pre-enzalutamide dosing

[s] ZEN003694 should be taken at the same time as enzalutamide starting on C1D1.

[t] Enzalutamide will be given as a single agent for 14 days (C1D -14 through -1) prior to the initiation of the combination therapy on C1D1 (Lead-in). The Lead-in period occurs only for Cycle 1 in DE-B and DC-B phases, and for those patients in DE-A or DC-A who are not currently taking enzalutamide and require the 14 day Lead-in. Enzalutamide should be taken once daily starting on C1D-14.

[u] Tumor assessment to include whole body radionuclide imaging (Tech-99) + cross-sectional imaging of the chest/abdomen/pelvis. Use of IV contrast is required unless contra-indicated. Magnetic resonance imaging (MRI) may be substituted for computed tomography (CT) per Investigator's discretion. Tumor assessment are to be performed during the Screening period, Cycle 3 Day 1 and every 3 cycles onward (C6D1, C9D1, etc.). Imaging may be scheduled up to 7 days prior to the scheduled clinic visit day.

[v] Physical examination, vital signs, hematology, coagulation tests, serum chemistry, urinalysis, ECG, tumor assessments, and/or other assessments may be performed as clinically indicated during any unscheduled visit

[w] At the End of Treatment if a subject's dose was held and treatment was not resumed after a two week period, the scheduling of the EOT visit from the date of last study drug is extended from 7 days to 14 days (±3 days).

[x] The Safety Follow-Up Visit should be completed 30 days (±3 days) after the End of Treatment visit or prior to the subject beginning a new anti-cancer treatment, whichever occurs first. If the subject begins a new anti-cancer treatment within 7 days following the End of Treatment visit, the Safety Follow-Up visit is not required.

[y] Blood samples (whole blood) for Exploratory BET inhibitor blood signature (**DC-A and DC-B**):

- C1D1: pre-ZEN003694 and enzalutamide doses
- C1D1: 4 hours (±15 min) post-ZEN003694 and enzalutamide doses
- C2D1: pre-ZEN003694 and enzalutamide doses

- C3D1: pre-ZEN003694 and enzalutamide doses
- Every 3 cycles onward (C6D1, C9D1, etc.): pre-ZEN003694 and enzalutamide doses
- End of Treatment Visit

[z] Urine samples for renal clearance of ZEN003694 and its metabolites for up to 8 hours may be collected at C1D15 upon direction from Zenith (DC Only)

[aa] Blood samples (whole blood) for exploratory cfDNA and ctDNA assessments

- C1D-14 pre- enzalutamide dose (**DE-B and DC-B and DE-A or DC-A Sub-Arm A2: all patients requiring the enzalutamide Lead-in**)
- C1D1 pre-ZEN003694 and enzalutamide doses
- C3D1 pre-ZEN003694 and enzalutamide doses
- End of Treatment Visit
- In selected patients who have shown evidence of response or progression, an unscheduled pre-dose sample may be collected during the course of the response based upon agreement between the Sponsor and Investigator

Table 2: PART 2 ONLY: ZEN003694 + Abiraterone

Schedule of Events – Dose Escalation (DE) and Dose Confirmation (DC)

	Screening (Within 28 Days of C1D-14 for DE-B and DC-B or C1D1 for DE-A and DC-A)	Cycle 1 (Days -14 through -1)	Cycle 1 (Days 1 – 28)	Cycle 2 (Days 1 – 28)	Cycle 3 Onward (Days 1 – 28)	Unscheduled Visit [v]	End of Treatment [w]	Safety Follow-up (30 Days after End of Treatment) [x]
Medical, Surgical, Malignancy History, Prior Cancer Treatments, Demographics	X							
Informed Consent	X							
Physical Examination, Weight, Height, ECOG Performance Status, Vital Signs [a]	X		Days 1, 8, 15, 22	Days 1, 15	Days 1	X	X	X
Hematology [b]	X	DE-D and DC-D: *Day -14 DE-C and DC-C Sub-arm C2^	Days 1*, 8, 15, 22	Days 1, 8, 15, 22	Days 1, 15	X	X	X
Coagulation Tests [c]	X	DE-D and DC-D: *Day -14 DE-C and DC-C Sub-arm C2^	Days 1*, 15	Day 1	Day 1	X		
Serum Chemistries [d]	X	DE-D and DC-D: *Day -14 DE-C and DC-C Sub-arm C2^	Days 1*, 8, 15, 22	Days 1, 8, 15, 22	Days 1, 15	X	X	X
Troponin [e]			Days 1, 15	Day 1	Day 1		X	
Serum Prostate-specific Antigen	X	DE-D and DC-D: *Day -14 DE-C and DC-C Sub-arm C2^	Day 1*	Day 1	Day 1		X	X
Urinalysis [f]	X	DE-D and DC-D: *Day -14 DE-C and DC-C Sub-arm C2^	Day 1*	Day 1	Day 1	X	X	X
Serum Testosterone	X		Day 1	Day 1	Day 1		X	X

	Screening (Within 28 Days of C1D-14 for DE-B and DC-B or C1D1 for DE-A and DC-A)	Cycle 1 (Days -14 through -1)	Cycle 1 (Days 1 – 28)	Cycle 2 (Days 1 – 28)	Cycle 3 Onward (Days 1 – 28)	Unscheduled Visit [v]	End of Treatment [w]	Safety Follow-up (30 Days after End of Treatment)[x]
Echocardiogram or Multigated Acquisition Scan [g]	X							
Triplicate 12-Lead Electrocardiogram [h]	X		Days 1, 15	Day 1	Day 1 [h]	X		
Ophthalmology Assessments[i]	X [i]					X [i]		
Qualitative Exploration of Visual Symptoms [i]		X	Day 1	Day 1			X	
Fresh Tumor and Archival Tumor Tissue Collection (Optional for DE, Mandatory for DC for Patients with Accessible Tumors)	X [j]				X [k]		X [l]	
Pharmacokinetics [m]			Days 1, 2, 15	Day 1				
BET Inhibitor Gene Expression Profile [n]			Days 1, 2					
Circulating Tumor Cells (CTCs) for Pharmacodynamic/Correlative Evaluation [o]		DE-D and DC-D: Day -14 DE-C and DC-C Sub-arm C2^	Day 1		Day 1 [o]		X	
CTCs for Enumeration/Response Analysis [p]		DE-D and DC-D: Day -14 DE-C and DC-C Sub-arm C2^	Day 1		Day 1 [p]		X	
Exploratory PD Biomarkers (DC Only) [q]		DC-D: Day -14 DC-C Sub-arm C2^	Day 1	Day 1			X	
ZEN003694 Administration [s]			Days 1 through 28 of each cycle					
Abiraterone Administration [t]		DE-D and DC-D: Days -14 through -1 DE-C and DC-C Sub-arm C2^	Days 1 through 28 of each cycle					
Adverse Events		DE-D and DC-D: Day -14	Days 1, 8, 15, 22	Days 1, 15	Day 1	X	X	X

	Screening (Within 28 Days of C1D-14 for DE-B and DC-B or C1D1 for DE-A and DC-A)	Cycle 1 (Days -14 through -1)	Cycle 1 (Days 1 – 28)	Cycle 2 (Days 1 – 28)	Cycle 3 Onward (Days 1 – 28)	Unscheduled Visit [v]	End of Treatment [w]	Safety Follow-up (30 Days after End of Treatment)[x]
		DE-C and DC-C Sub-arm C2^						
Prior/Concomitant Medications	X	DE-D and DC-D: Day -14 DE-C and DC-C Sub-arm C2^	Days 1, 8, 15, 22	Days 1, 15	Day 1	X	X	X
Tumor Assessment [u]	X				X [u]	X	X	
Exploratory BET Inhibitor Blood Signature (DC only) [y]			Day 1	Day 1	X [y]		X	
Exploratory cfDNA and ctDNA[aa]		DE-D and DC-D Day -14 DE-C and DC-C Sub-arm C2^	Day 1		Day 1		X	

Cycle 1 Day -14 Abiraterone Lead-in should begin -14 days ± 1 day from Cycle 1 Day 1. All other scheduled clinic attendance should occur within ± 3 days of the specified dates at all visits unless otherwise specified. Imaging for tumor assessments may be scheduled up to 7 days prior to the scheduled clinic visit day.

***** For patients requiring abiraterone Lead-in, perform laboratory tests at Cycle 1 Day -14 only if Screening visit tests were performed more than 7 days prior to the Cycle 1 Day -14 visit. For patients that do not require abiraterone Lead-in, perform laboratory tests at Cycle 1 Day 1 only if Screening visit tests were performed more than 7 days prior to the Cycle 1 Day 1 visit.

^ Only for patients in DE-C or DC-C who are not currently taking abiraterone, abiraterone is to be re-started with a 14 day Lead-in and Visit C1D-14 shall be conducted for applicable patients (DE-C or DC-C Sub-arm C2)

All assessments and tests/samples should be obtained pre-dose unless specified otherwise, and are to be performed even if dosing is not required (i.e., due to an on/off schedule) on the specified study visit day. Note: The visits in Cycle 2, on Days 8 and 22 and in Cycle 3 onward, on Day 15, will only include blood draws for safety laboratory testing and may be drawn after the patient has taken his dose (if dosing is required on that day).

Footnotes:

[a] Complete physical examination to be performed at the Screening visit and a symptom-directed physical examination thereafter. Height to be measured at the Screening Visit only. Vital signs: body temperature, blood pressure and heart rate.

[b] Hematology: complete blood count (CBC) with differential and absolute neutrophil count (ANC). Day 15 hematology can be waived at Investigator discretion starting in Cycle 6 onward as long as platelets are stable and there are no other laboratory concerns in the opinion of the Investigator.

[c] Coagulation tests: prothrombin time (PT) or international normalized ratio (INR) and partial thromboplastin time (PTT)

[d] Serum chemistry: albumin, alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase, amylase, bicarbonate, total bilirubin, blood urea nitrogen (BUN), total calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), lipase, sodium, potassium, phosphorus and magnesium. Note: Serum testosterone will be collected at screening, Day 1 of each cycle, and at EOT and Safety Follow-up. Day 15 serum chemistries can be waived at Investigator discretion starting in Cycle 6 onward as long as platelets are stable and there are no other laboratory concerns in the opinion of the Investigator.

[e] Troponin: serum samples will be drawn for analyses of troponin T and/or I proteins, based on local laboratory procedure. For any individual patient, the same method will be used at each timepoint.

[f] Urinalysis: dipstick with micro-analysis if clinically indicated.

[g] Cardiac echocardiogram or multigated acquisition (MUGA) scan for left ventricular ejection fraction

[h] Triplicate 12-lead electrocardiogram (ECG) to be performed as follows for each Part. For DE, DC-C and DC-D: Cycle 1 Day 1: pre-dose and 1 hour (±15 min) post-ZEN003694 and abiraterone doses; Cycle 1 Day 15: pre-dose and 1 hour (±15 min) post-ZEN003694 and abiraterone doses; Cycle 2 Day 1: pre-ZEN003694 and abiraterone doses; Cycle 3 Day 1 and every other cycle onward (C5D1, C7D1, etc.): pre-ZEN003694 and abiraterone doses.

[i] Ophthalmology assessments will be performed at Screening prior to C1D1 and after all entry criteria have been assessed and the subject is approved for enrollment in the study. At any time during the study should a clinically meaningful change in visual symptoms occur, repeat assessments are to be performed and may be recorded as an Unscheduled Visit. Ophthalmology assessments will include: Ophthalmic history, Snellen best corrected visual acuity (including refraction, if needed), color vision testing (using standard HRR pseudoisochromatic plates), pupillometry, OCT optic nerve and macula tests, fundus photography, and other exams as clinically indicated. The Visual Symptoms form (provided by the Sponsor) is to be administered by study personnel and completed at pre-dose on Cycle 1 Day-14, Cycle 1 Day 1, Cycle 2 Day 1 and at the EOT visit.

[j] Fresh tumor sample collections are optional and encouraged at Screening during the DE phase. Fresh tumor samples are mandatory at Screening during the DC phase for patients with accessible lesions. During each biopsy procedure, 2-4 tumor tissue cores (optimally 4 cores) should be obtained. For those patients in DE-C or DC-C who are not currently taking abiraterone and require 14 day Lead-in, the screening fresh tumor biopsy can be collected from time of consent through Cycle 1 Day -1, preferably during the 14 day abiraterone Lead-in. Archival tumor samples (initial diagnostic tissue or from prostatectomy or other resected tissue), if available and with the patient's consent, will be collected during the Screening period through the end of Cycle 2 or the End of Treatment, whichever occurs first.

[k] Fresh tumor sample collections at Cycle 3 Day 1 (± 15 days) during the DE phase are encouraged yet optional. Fresh tumor sample collections at Cycle 3 Day 1 (± 15 days) during the DC phase are mandatory if the tumor is accessible. During each biopsy procedure, 2-4 tumor tissue cores (optimally 4 cores) should be obtained.

[l] An optional biopsy will be taken at the time of disease progression by Prostate Cancer Working Group 2 (PCWG2) criteria for patients in the DE phase or DC phase of the study. Whenever possible, this biopsy should be performed while the patient is still receiving ZEN003694 and abiraterone, and 2 to 4 hours following administration of ZEN003694 and abiraterone on the day of biopsy.

[m] Blood (plasma) for pharmacokinetic (PK) profile of ZEN003694 and abiraterone and their active metabolites will be collected in **DE, DC-C and DC-D** as specified below:

- C1D1: pre-ZEN003964 and abiraterone doses
- C1D1: 15 min (±5 min), 30 min (±5 min), 1 hour (±5 min), 2 hours (±10 min), 4 hours (±15 min), 6 hours (±15 min) and 8 hours (±30 min) post-ZEN003694 and abiraterone doses
- C1D2: pre-ZEN003694 and abiraterone doses
- C1D15: pre-ZEN003964 and abiraterone doses
- C1D15: 15 min (±5 min), 30 min (±5 min), 1 hour (±5 min), 2 hours (±10 min), 4 hours (±15 min), 6 hours (±15 min) and 8 hours (±30 min) post-ZEN003694 and abiraterone doses
- C2D1: pre-ZEN003964 and abiraterone doses
- If abiraterone dose is reduced in DE any time after Cycle 1 or in DC at any time, optional PK samples are to be collected at the discretion of the sponsor following dose modification: pre-ZEN003964 and abiraterone doses, and 15 min (±5 min), 30 min (±5 min), 1 hour (±5 min), 2 hours (±10 min), 4 hours (±15 min), 6 hours (±15 min) and 8 hours (±30 min) post-ZEN003694 and abiraterone doses

[n] Blood samples (whole blood) for BET inhibitor gene expression profile:

- C1D1: pre-ZEN003694 and abiraterone doses
- C1D1: 2 hours (±15 min), 4 hours (±15 min), and 6 hour (±15 min) post-ZEN003694 and abiraterone doses
- C1D2: pre-ZEN003694 and abiraterone doses
- Unscheduled blood samples (whole blood) for BET inhibitor gene expression profile at pre-dose, 2 hours (±15 min), 4 hours (±15 min), and/or 6 hour (±15 min) post-ZEN003694 and abiraterone doses may also be drawn at later time-points, upon direction by Zenith

[o] Blood samples (whole blood) for CTCs for PD/correlative evaluation:

- C1D-14: pre-abiraterone dose (**for all patients requiring abiraterone Lead-in)**
- C1D1: pre-ZEN003694 and abiraterone doses

- C3D1: pre-ZEN003694 and abiraterone doses
- Every third cycle D1 (C6D1, C9D1, etc.): pre-ZEN003694 and abiraterone doses
- At disease progression and at the time of PSA or radiographic response

[p] Blood samples (whole blood) for CTCs for enumeration/response analysis:

- C1D-14: pre-abiraterone dose (**for all patients requiring abiraterone Lead-in**)
- C1D1: pre-ZEN003694 and abiraterone doses
- C3D1: pre-ZEN003694 and abiraterone doses
- Every third cycle D1 (C6D1, C9D1, etc.): pre-ZEN003694 and abiraterone doses
- At disease progression and at the time of PSA or radiographic response

[q] Blood samples (plasma) for exploratory PD assessments (**DC only**):

- C1D-14: pre-abiraterone dose (**for all patients requiring abiraterone Lead-in)**
- C1D1: pre-ZEN003694 and abiraterone doses
- C2D1: pre-ZEN003694 and abiraterone doses
- At study treatment discontinuation

[s] ZEN003694 should be taken at the same time as abiraterone starting on C1D1.

[t] Abiraterone will be given as a single agent for 14 days (C1D -14 through -1) prior to the initiation of the combination therapy on C1D1 (Lead-in). The Lead-in period occurs only for Cycle 1 in DE-D and DC-D phases, and for those patients in DE-C or DC-C who are not currently taking abiraterone and require the 14 day Lead-in. Abiraterone should be taken once daily starting on C1D-14.

[u] Tumor assessment to include whole body radionuclide imaging (Tech-99) + cross-sectional imaging of the chest/abdomen/pelvis. Use of IV contrast is required unless contra-indicated. Magnetic resonance imaging (MRI) may be substituted for computed tomography (CT) per Investigator's discretion. Tumor assessment are to be performed during the Screening period, Cycle 3 Day 1 and every 3 cycles onward (C6D1, C9D1, etc.). Imaging may be scheduled up to 7 days prior to the scheduled clinic visit day.

[v] Physical examination, vital signs, hematology, coagulation tests, serum chemistry, urinalysis, ECG, tumor assessments, and/or other assessments may be performed as clinically indicated during any unscheduled visit

[w] At the End of Treatment if a subject's dose was held and treatment was not resumed after a two week period, the scheduling of the EOT visit from the date of last study drug is extended from 7 days to 14 days (±3 days).

[x] The Safety Follow-Up Visit should be completed 30 days (±3 days) after the End of Treatment visit or prior to the subject beginning a new anti-cancer treatment, whichever occurs first. If the subject begins a new anti-cancer treatment within 7 days following the End of Treatment visit, the Safety Follow-Up visit is not required.

[y] Blood samples (whole blood) for Exploratory BET inhibitor blood signature (**DC-C and DC-D**):

- C1D1: pre-ZEN003694 and abiraterone doses
- C1D1: 4 hours (±15 min) post-ZEN003694 and abiraterone doses
- C2D1: pre-ZEN003694 and abiraterone doses
- C3D1: pre-ZEN003694 and abiraterone doses
- Every 3 cycles onward (C6D1, C9D1, etc.): pre-ZEN003694 and abiraterone doses
- End of Treatment Visit

[aa] Blood samples (whole blood) for exploratory cfDNA **and ctDNA assessments**

- C1D-14 pre- abiraterone dose **(DE-D and DC-D and DE-C or DC-C Sub-arm C2: all patients requiring abiraterone Lead-in**)
- C1D1 pre-ZEN003694 and abiraterone doses
- C3D1 pre-ZEN003694 and abiraterone doses
- End of Treatment Visit
- In selected patients who have shown evidence of response or progression, an unscheduled pre-dose sample may be collected during the course of the response based upon agreement between the Sponsor and Investigator

2. BACKGROUND

2.1 BET Inhibitors in Cancer

The bromodomain and extra terminal domain (BET) proteins comprise four closely related bromodomain-containing proteins (BRD2, BRD3, BRD4, and BRDT) that are a subset of the larger family of 46 bromodomain-containing proteins. The BET proteins are epigenetic readers that regulate transcription in part by binding acetylated lysines on histones and transcription factors. BET proteins have generated a lot of interest due to their potential to target the expression of oncogenes including V-Myc avian myelocytomatosis viral oncogene homolog (MYC), B-cell lymphoma 2 (BCL-2) and B-cell lymphoma 2-like 1 (BCL2L1) as well as for their involvement in mediating drug resistance (**Dawson, Kouzarides, & Huntly, 2012; Dawson et al., 2011; Goodell & Godley, 2013; Neff & Armstrong, 2013; Shi & Vakoc, 2014; Zuber et al., 2011**). Expression of multiple oncogenes is also driven by BRD4 recruitment at super-enhancers, providing a rationale for the activity of BET inhibitors (BETi) beyond the MYC family (**Hnisz et al., 2013**; **Loven et al., 2013**). All of the BETi currently in clinical trials target all members of the BET family, although the anti-proliferative activity of BETi in cancer cells may be mediated, in large part, through inhibition of BRD4 (**Filippakopoulos & Knapp, 2014**).

In vitro cell line analyses have shown that targeting BET proteins leads to inhibition of tumor growth in multiple cancer types, including both solid tumors and hematological malignancies through cell cycle arrest, and induction of senescence and apoptosis.

2.2 Rationale and Mechanism for BET Inhibitors in Metastatic Castration-resistant Prostate Cancer

Metastatic castration-resistant prostate cancer (mCRPC) is characterized by the persistence of signaling of the androgen receptor (AR) to drive cancer proliferation, tumor invasion, and metastasis (**Wyatt & Gleave, 2015**). Initial therapies of prostate cancer include either surgical or chemical castration, followed by androgen-deprivation therapy (ADT). In many instances, further progression and metastases of the cancer is observed, hence the term metastatic castration resistant prostate cancer. First line standard of care therapies for mCRPC include the AR antagonist enzalutamide, androgen synthesis inhibitors such as the cytochrome steroid 17-alpha-hydroxylase/17,20 lyase (CYP17A1) inhibitor abiraterone and in some cases chemotherapy. However, recent studies have shown that patients become resistant to these first line treatments over time and require additional drug therapy (**Wyatt & Gleave, 2015**). Currently, there is no standard of care for second line mCRPC as the efficacy of AR modulators or chemotherapy in the second line setting is moderate. Furthermore, it has been suggested that the resistance mechanisms of abiraterone and enzalutamide overlap (**Azad, Volik, et al., 2015; Bianchini et al., 2014; Loriot et al., 2013; Noonan et al., 2013; Schrader et al., 2014**).

Mechanisms of resistance to enzalutamide and abiraterone include alternative splicing of the AR resulting in the loss of the ligand binding domain and constitutively active androgen signaling (**Nakazawa, Antonarakis, & Luo, 2014**), up-regulation of alternate pathways such as glucocorticoid receptor (GR) (**Arora et al., 2013; Isikbay et al., 2014**), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (**Jin et al., 2013; Nadiminty et al., 2013**), or MYC signaling pathways (**Lamb, Massie, & Neal, 2014; Nadiminty et al., 2013; Zeng et al., 2015**), as well as neuroendocrine differentiation (**Aggarwal, Zhang, Small, & Armstrong, 2014; Beltran et al., 2014; Dang et al., 2015**). Several of these resistance mechanisms, have either been shown to be regulated by the BET proteins in prostate cancer (MYC expression: (**Gao et al., 2013**) AR splice variants: **(S. C. Chan et al., 2015**); GR: (**Shah et al., 2015**) or in other cancers, NF-κB: **(Ceribelli et al., 2014; Gallagher et al., 2014; Zou et al., 2014**)), suggesting that BETi could be beneficial for patients with mCRPC that are resistant to enzalutamide and abiraterone. In particular, the androgen receptor splice variant 7 (AR-V7) was recently suggested to be involved in the resistance to enzalutamide and abiraterone (**Antonarakis et al., 2014**), and cell lines expressing these variants are sensitive to ZEN003694 and other BETi in culture and in xenografts (**Asangani et al., 2014; S. C. Chan et al., 2015; Gao et al., 2013; Wyce et al., 2013**). One of the proposed mechanisms of action of the BETi is to prevent the BET proteins from interacting with the N-terminus of the AR and activating downstream androgen signaling pathways (**Asangani et al., 2014**). This mechanism would also explain how the activity of ZEN003694 would not be abrogated by the AR splice variants, as the N-terminus is still intact. Also, BETi prevent binding of the AR to their downstream effectors, including the E26 transformation-specific (ETS) family of proteins (e.g., ETV1 and ERG), well known oncogenic drivers in prostate adenocarcinoma and neuroendocrine prostate cancer (**Gasi Tandefelt, Boormans, Hermans, & Trapman, 2014; Lotan et al., 2011; Williamson et al., 2011**), thus providing several possible mechanisms whereby BETi could act in patients with prostate cancers of different etiologies.

BETi are also postulated to be good combination agents due to their novel involvement in the transcriptional up-regulation of several key oncogenic pathways (**Hnisz et al., 2013**). In mCRPC, the combination of BETi with enzalutamide could further abrogate AR signaling and inhibit tumor progression. Several clinical studies have reported that enzalutamide treatment of post-abiraterone patients elicits a poor to moderate response rate (**Azad, Eigl, Murray, Kollmannsberger, & Chi, 2015; Bianchini et al., 2014; Loriot et al., 2013; Noonan et al., 2013; Schrader et al., 2014**), supporting the evaluation of BETi such as ZEN003694 in post-abiraterone patients, either as a single agent, or in combination with enzalutamide.

Recent preclinical studies have suggested that SPOP mutant CRPC might be less sensitive to BETi, mainly due to the upregulation of the BET proteins, which are natural substrates of the SPOP ubiquitin ligase **(Dai et al., 2017; Janouskova et al., 2017; P. Zhang et al., 2017).** However, SPOP is also involved in DNA damage repair **(D. Zhang et al., 2014),** and SPOP mutations were found to activate AR and PI3K/mTOR signaling **(Blattner et al., 2017)** and lead to genomic instability **(Boysen et al., 2015).** Therefore, it remains to be determined if this

altered sensitivity is also found in the clinic, and more importantly, if combination with either enzalutamide or abiraterone could be beneficial in that patient population.

2.3 ZEN003694

ZEN003694 is a structurally novel, orally bioavailable small molecule that epigenetically regulates gene expression through bromodomain and extra-terminal domain (BET) inhibition. [redacted] ZEN003694 was discovered and developed by Zenith Epigenetics Ltd. and has broad potential as an anti-proliferative agent in solid tumors and hematologic malignancies.

2.4 Nonclinical Data

For full information regarding ZEN003694, refer to the Investigator's Brochure.

ZEN003694 and its major active metabolite, ZEN003791, bind BET bromodomains and selectively inhibit the BET family member BRD4 binding to super-enhancers in chromatin, in turn inhibiting expression of BRD4-dependent genes MYC and BCL-2 family members that drive proliferation and inhibit apoptosis of cancer cells. ZEN003694 and ZEN003791 were equipotent biochemically and in cell assays. [redacted] Based on extensive in vitro binding studies, ZEN003694 and ZEN003791 are considered to have low potential for off-target pharmacologic effects.

ZEN003694 showed potent cell growth inhibition in multiple solid tumor and hematological cancer cell lines as a single agent, and displayed synergy or additivity when combined with different anti-cancer agents. In castration-resistant prostate cancer (CRPC) cell lines that were insensitive to enzalutamide, ZEN003694 showed potent activity as a single agent and synergy in combination with enzalutamide in a cell line with mild sensitivity to enzalutamide.

In vivo preclinical data demonstrated that ZEN003694 dose-dependently inhibited tumor growth and MYC gene expression in CRPC (VCaP and 22Rv1) cell line-derived subcutaneous mouse xenografts. ZEN003694 was well tolerated at the dose range tested (up to 100 mg/kg [redacted] [QD]) and robustly inhibited the expression of MYC in xenograft tumors. ZEN003694 was also evaluated in combination with enzalutamide in these xenograft mouse models. VCaP cells are sensitive while 22Rv1 are resistant to enzalutamide treatment.

In the 22Rv1 xenograft model, ZEN003694 exhibited robust tumor growth inhibition (TGI), which was significantly more efficacious than that of enzalutamide. The combination was well tolerated and based on the administered doses (mg/kg), there was no improvement in efficacy

with ZEN003694 in combination with enzalutamide versus ZEN003694 alone. However, as the presence of enzalutamide reduced the exposure of ZEN003694, an analysis was done to correlate percent TGI versus exposure of mice (combined area under the curve $[AUC]_{0-24}$ of ZEN003694 and its active metabolite ZEN003791), rather than dose. On an exposure basis, the anti-tumor effects of ZEN003694 and enzalutamide appear to be additive. In the VCaP xenograft model, ZEN003694 TGI, which was equivalent to that of enzalutamide.

In addition, ZEN003694 showed robust dose-dependent inhibition of tumor growth, with good systemic exposure and inhibition of MYC gene expression in xenograft tumors derived from acute myeloid leukemia (AML). In xenograft tumors derived from triple negative breast cancer (TNBC), ZEN003694 showed robust dose-dependent inhibition of tumor growth, with good systemic exposure, but did not appear to down-regulate MYC gene expression.

These results suggest that ZEN003694 inhibits persistent AR signaling even in cases associated with resistance to enzalutamide or abiraterone therapies, and inhibits tumor growth in prostate cancer in vivo models that are either resistant or sensitive to enzalutamide. These data provide a rationale for studying ZEN003694 in combination with either enzalutamide or abiraterone in mCRPC patients who are likely to benefit from treatment.

In general, the nonclinical pharmacokinetics (PK) of ZEN003694 were similar between species. ZEN003694 showed rapid absorption in all species evaluated following oral dosing. In rats, absorption was nearly complete within 0.5 hour of dosing, followed by elimination half-lives ranging from 1 to 2 hours. [redacted].

ZEN003694 metabolism in vitro was predominantly through CYP3A4 [redacted] ZEN003694 and ZEN003791 are not inducers or inhibitors of CYP enzymes. [redacted]

To support the initial Phase 1 clinical studies of ZEN003694 in patients with mCRPC, Zenith conducted a non-Good Laboratory Practice (GLP) Ames assay, a GLP human ether-à-go-go related gene (hERG) assay, and GLP-compliant 28-day repeat-dose general toxicology studies in rats and monkeys. The rat and cynomolgus monkey were selected as appropriate species due to their similarity of metabolite profile in humans based on liver microsomes metabolic stability. [redacted]

[redacted]

Most adverse effects observed in the toxicology studies were considered likely to be mechanism-based or sequelae; all significant adverse effects were considered to be discernable by clinical evaluation, physical examination, and/or standard laboratory analyses and medically manageable. ZEN003694 did not inhibit hERG in patch-clamp assays and did not have an effect on the standard 10-lead electrocardiographic evaluations in the GLP compliant toxicology study in monkey. ZEN003694 did not have any functional effect in respiratory and central nervous system (CNS) assessments at any dose level in the GLP-complaint toxicology studies. Furthermore, ZEN003694 was negative in the Ames mutagenicity study.

Based on the nonclinical profile, results from animal toxicology studies and the structural compound, theoretical risks of human exposure to ZEN003694 include the following:

- Anorexia and weight loss
- Nausea and other gastrointestinal symptoms
- Myelosuppression (with consequences of anemia, neutropenia and/or thrombocytopenia)
- Susceptibility to infection
- Bleeding
- Aberrations in clinical chemistry parameters

Other drugs with similar mechanism of action, to the extent they have been studied in the clinic, have been associated with adverse events of diarrhea, nausea, vomiting, anorexia, rash, asthenia, thrombocytopenia, neutropenia, anemia, dysgeusia, fever, hyperglycemia, mucositis, coagulopathy, hemorrhage and aberrations of clinical chemistry parameters (**Thieblemont et al., 2014**).

2.5 Clinical Data

Based on data collected through the end of December 2017, the combined Phase 1 clinical data (44 patients) reported to date across both studies (this study and the **ZEN003694-001** Single Agent Study) have identified the following adverse drug reactions (drug related and occurring in > 2 patients): visual impairment (typically a transitory perception of brighter lights and/or light flashes, with or without visual color tinges, and with no functional consequences), nausea, fatigue, decreased appetite, vomiting, creatinine increase, platelet decrease, diarrhea, dehydration, decreased weight, dizziness, dysgeusia, and thrombocytopenia. These ZEN003694-related adverse events (AEs) were generally Grade 1 or 2 in severity, were managed clinically, did not result in long-term sequelae, and resolved in the absence of drug exposure.

[redacted]

[redacted]

2.6 Study Rationale

Several studies using cell lines and xenografts in prostate cancer have shown that BET proteins interact with the AR to modulate AR signaling. BETi were shown to induce apoptotic activity, and inhibit cell proliferation and tumor growth of different CRPC models (**Asangani et al., 2014; C. H. Chan et al., 2015; Cho et al., 2014; Gao et al., 2013; Wyce et al., 2013**). Furthermore, recent studies have shown that the BET proteins are directly involved in resistance mechanisms to ARSI (**Shah et al., 2017**)

ZEN003694 inhibits proliferation in several prostate cancer cell lines as well as in cell lines resistant to the ARSIs enzalutamide and abiraterone. ZEN003694 also inhibits AR signaling in cells expressing high ratios of the AR-V7 (22Rv1) splice variant compared to the full-length AR, which lack the androgen binding domain and results in constitutive activation of AR signaling. Pre-clinical in vitro data also show that ZEN003694 synergizes with enzalutamide in inhibiting cell growth of a CRPC cell line and synergizes with abiraterone to inhibit the proliferation of a different CRPC cell line.

In vivo preclinical data demonstrate that ZEN003694 dose-dependently inhibited tumor growth in CRPC (VCaP and 22Rv1) cell line-derived subcutaneous mouse xenografts. ZEN003694 was well tolerated at the dose range tested (up to 100 mg/kg q.d.) and robustly inhibited the expression of MYC in xenograft tumors. ZEN003694 was also evaluated as a single agent and in combination with enzalutamide in the CRPC (VCaP and 22Rv1) xenograft mouse models. VCaP cells are sensitive while 22Rv1 are resistant to enzalutamide treatment. In the VCaP xenograft model, ZEN003694 showed robust dose-dependent efficacy and was equivalent to the efficacy of enzalutamide. In the 22Rv1 xenograft model, ZEN003694 had robust efficacy and was more efficacious than enzalutamide.

In the 22Rv1 model, the combination treatment of ZEN003694 and enzalutamide was evaluated at limited dose range combinations. The combination was well tolerated and based on TGI normalized to the combination exposures of ZEN003694 and the active metabolite ZEN003791 showed an additive effect at the evaluated concentrations.

The in vivo models evaluated are limited in their capabilities to assess the combined effect of ARSIs and ZEN003694 as they do not necessarily represent the study populations: (1) enzalutamide-naïve patients that have progressed on abiraterone (or vice-versa) and (2) patients taking an ARSI and progressing by PCWG2 criteria. Despite the limitations of these models, the data show that ZEN003694 is active in a model that is resistant to enzalutamide and

has equivalent activity to enzalutamide in an enzalutamide-sensitive model. The data also show that the effect of enzalutamide and ZEN003694 is additive in an enzalutamide resistant model.

In summary, these results suggest that ZEN003694 inhibits persistant AR signaling even in cases associated with resistance to ARSI therapies, and inhibits tumor growth in prostate cancer in vivo models that are either resistant or sensitive to enzalutamide. These data provide a rationale for studying ZEN003694 in combination with either enzalutamide or abiraterone in mCRPC patients who are likely to benefit from treatment.

2.7 Dosing Rationale

The safe starting dose of ZEN003694 was determined in concordance with the International Conference on Harmonization (ICH) S9 Guidance. Zenith has calculated the starting dose for ZEN003694 in the Phase 1 single agent study, ZEN003694-001, from the toxicology studies, that were dosed on a mg/kg basis, to derive a flat dose (48 mg) for the initial starting dose of ZEN003694 in this first-in-human (FIH) Phase 1 study.

[redacted]

[redacted]

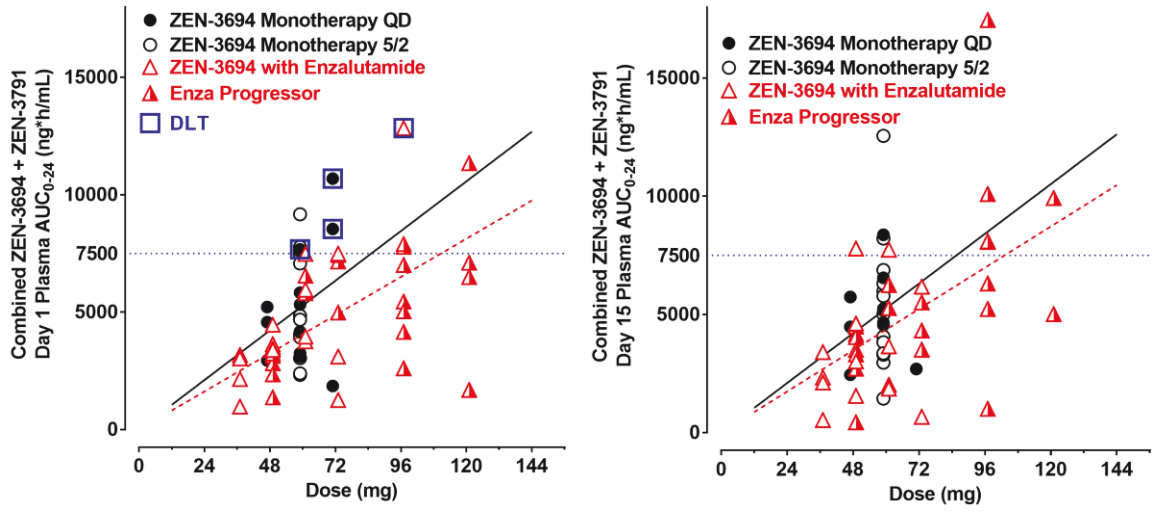
Part 1: The starting dose of ZEN003694 in this combination treatment study, ZEN003694-002, is therefore being selected as 36mg/day [redacted] The dose of enzalutamide will be held constant at 160 mg/day through Cycle 1 of the study in Dose Escalation. Furthermore, since enzalutamide is a CYP3A4 inducer and ZEN003694 is a substrate of CYP3A4, the plasma concentration of ZEN003694 dosed in combination with enzalutamide is expected to be lower than single agent administration at equivalent doses of ZEN003694. The dose of 36 mg/day is expected to produce tolerable exposure while being close to the therapeutic range. Finally no overlapping toxicities are expected with ZEN003694 in combination with enzalutamide further justifying the starting dose.

Part 2:
Based on the safety and PK/PD data from the ongoing investigation of Part 1 of the current

study, ZEN003694 in combination with enzalutamide, a reasonable ZEN003694 dose to initiate this combination trial is 72 mg QD for ZEN003694 in combination with 1000 mg QD abiraterone. [redacted] the dose of 96 mg QD in Part 1 was tolerated in the current combination study, with one DLT (of grade 2 nausea) out of six patients. Dosing at 120 mg QD has also been tolerated by a cohort of three patients in Part 1, ZEN003694 plus enzalutamide, and a dose of 144mg QD is being investigated at the time of this amendment. [redacted] Abiraterone is not a CYP3A4 inducer and is not expected to induce a higher ratio of the ZEN003694 active metabolite to parent in Part 2 of this study; but in the setting of anticipatory management of adverse gastrointestinal effects, it is expected that 72 mg of ZEN003694 will be tolerated in combination with 1000 mg abiraterone.

In case of DLTs and clinically significant AEs, dose holds and reductions are allowed where applicable by this protocol. Proactive management of nutrition, hydration, and anti-emetics will also be implemented in Part 2 of this study, and pharmacokinetic monitoring will allow management of systemic exposure within known tolerated levels.

The correlation of DLT events with patient exposure at Cycle 1 Day 1 and Cycle 1 Day 15 across both monotherapy and combination therapy studies is shown in the figure below.



The data show that DLT events occurred in patients with exposures (ZEN003694 + ZEN003791) greater than approximately 7500 ng*h/ml. The data also show that the PK interaction with enzalutamide has been minimal and the exposures of ZEN003694 + ZEN003791 were not significantly impacted by enzalutamide. The average exposure at the 72 mg dose in the single agent and the combination with enzalutamide study is 5250 ng*h/ml and less than 7500 ng*h/ml, and also less than the Day 1 average AUC_{0-24} of 7048 ng*h/ml reported at the 96mg dose. Therefore, starting at a dose of 72 mg QD is reasonable for ZEN003694 in combination with abiraterone. Abiraterone is not expected to affect the exposure of ZEN003694 based on its CYP profile.

Integrated data on PK and safety to date supports the use of 72 mg as the starting dose for the ZEN003694 + abiraterone combination study. Given that the maximum tolerated human dose of ZEN003694 as monotherapy and in combination with enzalutamide will both be determined before dose-escalation starts in Part 2 of this trial, dose-escalation of ZEN003694 in combination with abiraterone may not be sought in Part 2.

3. OBJECTIVES

3.1 PART 1 OBJECTIVES: ZEN003694 in combination with enzalutamide

3.1.1 Part 1: Primary

- To determine the safety, tolerability and maximum tolerated dose (MTD) of ZEN003694 in combination with enzalutamide in patients with mCRPC who have progressed during prior treatment with enzalutamide or apalutamide (Cohort DE-A) or with abiraterone (Cohort DE-B) by Prostate Cancer Working Group 2 (PCWG2) criteria 2007 (**Scher et al., 2008**) (dose escalation)

- To confirm the safety and tolerability of the MTD and recommended Phase 2 dose (RP2D) of ZEN003694 in combination with enzalutamide in the following two cohorts of patients with mCRPC (dose confirmation):

  - Cohort DC-A: Patients with prior progression on enzalutamide or apalutamide by PCWG2 criteria who are currently or will be receiving a stable dose of enzalutamide

  - Cohort DC-B: Patients who are enzalutamide-naïve with prior progression on abiraterone by PCWG2 criteria

3.1.2 Part 1: Secondary

- To determine the PK of ZEN003694 and the PK of enzalutamide along with their primary active metabolites when administered in combination

- To evaluate the preliminary clinical activity of ZEN003694 in combination with enzalutamide as applicable:

  - PSA response rate by PCWG2 criteria
  - Radiographic response rate by PCWG2 criteria
  - Median progression-free survival by PCWG2 criteria
  - Circulating tumor cell (CTC) response rate

3.1.3 Part 1: Exploratory

- To explore pharmacodynamics (PD), prognostic and/or predictive biomarkers of ZEN003694 in combination with enzalutamide in whole blood, plasma and tumor samples in the dose escalation phase and/or dose confirmation phase as follows:

  - Possible relationship of baseline tumor abnormalities (such as mutations, translocations, mRNA, protein expression and localization), in circulating tumor DNA (ctDNA), circulating tumor cells (CTC) and tumor biopsies and/or on-treatment changes with any observed antitumor activity

- To explore the effects of ZEN003694 on immuno-oncology markers in tumor tissue and peripheral blood mononuclear cells

3.2 PART 2 OBJECTIVES: ZEN003694 in combination with abiraterone

3.2.1 Part 2: Primary

- To determine the safety, tolerability and recommended Phase 2 dose (RP2D) of ZEN003694 in combination with abiraterone in patients with metastatic castration-resistant prostate cancer (mCRPC) who have progressed during prior treatment with abiraterone (Cohort DE-C) or enzalutamide or apalutamide (Cohort DE-D) by Prostate Cancer Working Group 2 criteria 2007 (**Scher et al., 2008**) (dose escalation)

- To confirm the safety and tolerability of the recommended Phase 2 dose (RP2D) of ZEN003694 in combination with abiraterone in the following two cohorts of patients with mCRPC (dose confirmation):

  - Cohort DC-C: Patients currently receiving abiraterone who have experienced progression by PCWG2 criteria

  - Cohort DC-D: Patients who are abiraterone-naïve with prior progression on enzalutamide or apalutamide by PCWG2 criteria

3.2.2 Part 2: Secondary

- To determine the PK of ZEN003694 and the PK of abiraterone along with their primary active metabolites when administered in combination

- To evaluate the preliminary clinical activity of ZEN003694 in combination with abiraterone as applicable:

  - PSA response rate by PCWG2 criteria
  - Radiographic response rate by PCWG2 criteria
  - Median progression-free survival by PCWG2 criteria
  - Circulating tumor cell (CTC) response rate

3.2.3 Part 2: Exploratory

- To explore pharmacodynamics (PD), prognostic and/or predictive biomarkers of ZEN003694 in combination with abiraterone in whole blood, plasma and tumor samples in the dose escalation phase and/or dose confirmation phase as follows:

  - Possible relationship of baseline tumor abnormalities (such as mutations, translocations, mRNA, protein expression and localization), in circulating tumor DNA (ctDNA), circulating tumor cells (CTC) and tumor biopsies and/or on-treatment changes with any observed antitumor activity

4. PATIENT SELECTION

4.1 Part 1: ZEN003694 in combination with enzalutamide

4.1.1 Part 1: Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for the study.

Part 1 All Patients

1. Males age ≥ 18 years
2. Metastatic, castrate resistant histologically confirmed prostate cancer; surgically castrated or continuous medical castration for ≥ 8 weeks prior to screening
3. Serum testosterone < 50 ng/dL determined within 4 weeks of first administration of study drug
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
5. Adequate laboratory parameters at Screening including:
   a. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
   b. Platelet count ≥ 100,000/mm^3
   c. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤ 2.0 x ULN (≤ 5 x ULN if liver metastases are present)
   d. Total bilirubin ≤ 1.25 x ULN
   e. Serum creatinine ≤ 1.5 x ULN or calculated (Cockcroft-Gault formula) or measured creatinine clearance ≥ 60 mL/min
   f. Prothrombin time (PT), international normalized ratio (INR) and partial thromboplastin time (PTT) < 1.5 x ULN
6. Use of corticosteroids is allowed up to a daily dose of 10 mg prednisone or equivalent provided that the dose has been stable for at least 2 weeks prior to first administration of study drug and will remain stable during study drug and enzalutamide dosing
7. Patients must be surgically sterile or must agree to use physician-approved contraception during the study and for 30 days following the last study drug administration
8. Ability to swallow capsules and comply with study procedures
9. Ability to understand and willingness to sign informed consent form prior to initiation of any study procedures

Part 1 Dose Escalation

10. Cohort DE-A: Prior progression on enzalutamide or apalutamide at any time by PCWG2 criteria and is or will be receiving a stable dose of enzalutamide (defined as a dose that has not changed for at least 2 weeks prior to Cycle 1 Day 1 and is not expected to change on study). Patients may or may not have experienced prior progression on abiraterone.

11. Cohort DE-B: Enzalutamide-naïve and apalutamide-naïve patients following prior progression on abiraterone by PCWG2 criteria

Part 1 Dose Confirmation

12. Cohort DC-A: Prior progression on enzalutamide or apalutamide at any time by PCWG2 criteria and is or will be receiving a stable dose of enzalutamide (defined as a dose that has not changed for at least 2 weeks prior to Cycle 1 Day 1 and is not expected to change on study). Patients may or may not have experienced prior progression on abiraterone.

13. Cohort DC-B: Enzalutamide-naïve patients and apalutamide-naïve following prior progression on abiraterone by PCWG2 criteria.

4.1.2 Part 1: Exclusion Criteria

Patients who meet any of the following exclusion criteria will not be eligible to participate in the study.

Part 1 All Patients

1. Any history of brain metastases or prior seizure or conditions predisposing to seizure activity

2. Have previously received an investigational BET inhibitor (including previous participation in this study or Study **ZEN003694-001**)

3. Have received prior systemic anti-cancer therapy (including abiraterone) or investigational therapy within 2 weeks or five half-lives, whichever is shorter, prior to the first administration of study drug

4. Failure to recover to Grade 1 or lower toxicity related to prior systemic therapy (excluding alopecia and neuropathy) prior to study entry

5. Radiation therapy within 2 weeks of the first administration of study drug

6. Treatment with a bone-targeted radionuclide within 6 weeks of first administration of study drug (enzalutamide in DE-B and DC-B or ZEN003694 in DE-A and DC-A)

7. Have received prior chemotherapy in the metastatic castration-resistant setting (prior chemotherapy in the hormone-sensitive setting is allowed provided last dose was at least 6 months prior to study entry)

8. Have received prior investigational anti-androgen therapy

9. Currently receiving medications known to be strong inhibitors of CYP2C8, strong inducers (except enzalutamide or apalutamide) or inhibitors of CYP3A4 and substrates of CYP1A2, CYP3A4, CYP2C9 and CYP2C19 with a narrow therapeutic window. See Section **6.8.1**. Strong inducers, inhibitors and substrates must be discontinued at least 7 days prior to the first administration of study drug.

10. Not a candidate for enzalutamide treatment, in the opinion of the Investigator

11. Left ventricular ejection fraction less than the lower of 50% or the lower limit of institution's normal range

12. QTcF interval > 450 msec

13. Known impaired cardiac function or clinically significant cardiac disease such as uncontrolled supraventricular arrhythmia, ventricular arrhythmia requiring therapy, or congestive heart failure (New York Heart Association functional class III or IV)

14. Myocardial infarction or unstable angina within 6 months prior to the first administration of study drug

15. Other clinically significant co-morbidities, such as uncontrolled pulmonary disease, active CNS disease, active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy, or any other condition that could compromise safety or the patient's participation in the study

16. Other known active cancer requiring therapy at time of study entry

17. Historically positive (screening tests not required) for human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) or with active infections. HBV positivity defined by positive hepatitis B surface antigen (HBsAg). HCV positivity defined as positive HCV viral load.

18. Major surgery other than diagnostic surgery, dental surgery or stenting within 4 weeks prior to the first administration of study drug

19. History of congenital or other deficiency in platelet function, any known inherent or acquired coagulopathy, or therapeutic anticoagulation with warfarin or apixaban (low-dose warfarin for port patency or prophylactic anti-platelet agents are allowed)

20. Concurrent participation in another clinical investigational treatment trial

21. Any other reason that in the opinion of the Investigator would prevent the patient from completing participation or following the study schedule

4.2 Part 2: ZEN003694 in combination with abiraterone

4.2.1 Part 2: Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for the study.

Part 2 All Patients

1. Males age ≥ 18 years
2. Metastatic, castrate resistant, histologically confirmed prostate cancer; surgically castrated or continuous medical castration for ≥ 8 weeks prior to screening
3. Serum testosterone < 50 ng/dL determined within 4 weeks of first administration of study drug
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
5. Adequate laboratory parameters at Screening including:
    a. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
    b. Platelet count ≥ 100,000/mm^3
    c. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤ 2.0 x ULN (≤ 5 x ULN if liver metastases are present)
    d. Total bilirubin ≤ 1.25 x ULN
    e. Serum creatinine ≤ 1.5 x ULN or calculated (Cockcroft-Gault formula) or measured creatinine clearance ≥ 60 mL/min
    f. Prothrombin time (PT), international normalized ratio (INR) and partial thromboplastin time (PTT) < 1.5 x ULN
6. Use of corticosteroids is allowed up to a daily dose of 10 mg prednisone or equivalent provided that the dose has been stable for at least 2 weeks prior to first administration of study drug and will remain stable during study drug and abiraterone dosing
7. Patients must be surgically sterile or must agree to use physician-approved contraception during the study and for 30 days following the last study drug administration
8. Ability to swallow capsules and comply with study procedures
9. Ability to understand and willingness to sign informed consent form prior to initiation of

any study procedures

Part 2 Dose Escalation

10. Cohort DE-C: Prior progression on abiraterone at any time by PCWG2 criteria and is or will be receiving a stable dose of abiraterone (defined as a dose that has not changed for at least 2 weeks prior to Cycle 1 Day 1 and is not expected to change on study). Patients may or may not have experienced prior progression on enzalutamide or apalutamide.

11. Cohort DE-D: Abiraterone-naïve patients following prior progression on enzalutamide or apalutamide by PCWG2 criteria.

Part 2 Dose Confirmation

12. Cohort DC-C: Prior progression on abiraterone at any time by PCWG2 criteria and is or will be receiving a stable dose of abiraterone (defined as a dose that has not changed for at least 2 weeks prior to Cycle 1 Day 1 and is not expected to change on study). Patients may or may not have experienced prior progression on enzalutamide or apalutamide.

13. Cohort DC-D: Abiraterone-naïve patients following prior progression on enzalutamideor apalutamide by PCWG2 criteria.

4.2.2 Part 2: Exclusion Criteria

Patients who meet any of the following exclusion criteria will not be eligible to participate in the study.

Part 2 All Patients

1. Have previously received an investigational BET inhibitor (including previous participation in this study or Study **ZEN003694-001**)

2. Have received prior systemic anti-cancer therapy or investigational therapy within 2 weeks or five half-lives, whichever is shorter, prior to the first administration of study drug. (Patients progressing on enzalutamide or apalutamide require a 2 week wash-out prior to start of abiraterone Cycle 1 Lead-in where applicable)

3. Failure to recover to Grade 1 or lower toxicity related to prior systemic therapy (excluding alopecia and neuropathy) prior to study entry

4. Radiation therapy within 2 weeks of the first administration of study drug

5. Treatment with a bone-targeted radionuclide within 6 weeks of first administration of study drug (abiraterone in DE-D and DC-D or ZEN003694 in DE-C and DC-C)

6. Have received prior chemotherapy in the metastatic castration-resistant setting (prior chemotherapy in the hormone-sensitive setting is allowed provided last dose was at least

6 months prior to study entry)

7. Have received prior investigational anti-androgen therapy
8. Currently receiving medications known to be substrates of CYP1A2 or CYP2D6 with a narrow therapeutic window. Major substrates must be discontinued at least 7 days prior to the first administration of study drug.
9. Not a candidate for abiraterone treatment, in the opinion of the Investigator
10. Left ventricular ejection fraction less than the lower of 50% or the lower limit of institution's normal range
11. QTcF interval > 450 msec
12. Known impaired cardiac function or clinically significant cardiac disease such as uncontrolled supraventricular arrhythmia, ventricular arrhythmia requiring therapy, or congestive heart failure (New York Heart Association functional class III or IV)
13. Myocardial infarction or unstable angina within 6 months prior to the first administration of study drug
14. Other clinically significant co-morbidities, such as uncontrolled pulmonary disease, active central nervous system disease, active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy, or any other condition that could compromise safety or the patient's participation in the study
15. Other known active cancer requiring therapy at time of study entry
16. Historically positive (screening tests not required) for human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) or with active infections. HBV positivity defined by positive hepatitis B surface antigen (HBsAg). HCV positivity defined as positive HCV viral load
17. Major surgery other than diagnostic surgery, dental surgery or stenting within 4 weeks prior to the first administration of study drug
18. History of congenital or other deficiency in platelet function, any known inherent or acquired coagulopathy, or therapeutic anticoagulation with warfarin or apixaban (low-dose warfarin for port patency or prophylactic anti-platelet agents are allowed)
19. Concurrent participation in another clinical investigational treatment trial
20. Any other reason that in the opinion of the Investigator would prevent the patient from completing participation or following the study schedule

5. STUDY PLAN

5.1 Study Design

This is an open label, non-randomized, Phase 1 dose escalation/dose confirmation study of ZEN003694 in combination with enzalutamide (Part 1) or abiraterone (Part 2) in patients with mCRPC.

5.1.1 Dose Escalation

A standard 3+3 cohort design will be utilized for each study Part. Cohorts of up to 6 patients will be enrolled at each dose level, and each patient will participate in only one cohort. Each cycle will be 28 days in duration.

Part 1, ZEN003694 in combination with enzalutamide:
For patients who have progressed on abiraterone, (Cohort DE-B) enzalutamide will be administered orally as a single agent daily for 14 days prior to the initiation of the combination therapy (Lead-in) to reach enzalutamide steady-state concentration (C_{ss}) during Cycle 1. After the Lead-in, if applicable, ZEN003694 will be administered orally in combination with daily enzalutamide for 28-day cycles. Patients who are progressing on enzalutamide or apalutamide (Cohort DE-A, Sub-arm A1) and who are currently receiving a stable dose of enzalutamide will continue to receive enzalutamide in combination with ZEN003694, if eligibility criteria are met. Patients in Cohort DE-A who are not currently receiving enzalutamide or apalutamide or are currently taking apalutamide (Sub-arm A2) will be administered enzalutamide orally once daily for 14 days prior to the initiation of the combination therapy (Lead-in) to reach enzalutamide C_{ss} during Cycle 1.

Part 2, ZEN003694 in combination with abiraterone:
For patients who have progressed on enzalutamide or apalutamide (Cohort DE-D), abiraterone will be administered orally as a single agent daily for 14 days prior to the initiation of the combination therapy (Lead-in) to reach abiraterone steady-state concentration (C_{ss}) during Cycle 1. After the Lead-in, if applicable, ZEN003694 will be administered orally in combination with daily abiraterone for 28-day cycles. Patients who are progressing on abiraterone (Cohort DE-C, Sub-arm C1) and currently receiving a stable dose of abiraterone will continue to receive abiraterone in combination with ZEN003694, if eligibility criteria are met. For patients who have progressed on abiraterone (Cohort DE-C, Sub-Arm C2) but are not currently taking abiraterone, abiraterone will be administered orally as a single agent daily for 14 days prior to the initiation of the combination therapy (Lead-in) to reach abiraterone steady-state concentration (C_{ss}) during Cycle 1.

Part 1 and Part 2:
After the Lead-in, ZEN003694 will be administered orally in combination with daily enzalutamide (Part 1) or abiraterone (Part 2) for 28-day cycles. The first patient at each dose level will be treated with ZEN003694 for one week before the second patient at the same dose

level is allowed to receive their first dose of ZEN003694. Patients at each dose level will be treated (for 28 days) and observed through the end of the first cycle before treatment of patients at the next higher dose level can begin. In unusual circumstances, (e.g., if there is 1 slot remaining to fill a cohort and 2 prospective enrollees are being screened and qualify simultaneously) the sponsor may allow an extra subject to enter a cohort, although the same rules for determining MTD will apply.

ZEN003694-related adverse events (AEs) for determination of DLTs will be assessed for each patient during the 28 days of Cycle 1. The most common AEs for enzalutamide and abiraterone are well-known (see **Appendix 4** for XTANDI® Package Insert and **Appendix 5** for ZYTIGA® Package Insert). As such, the Investigator should to the best of his/her ability assess the relatedness of an AE observed as attributable to either enzalutamide (Part 1) or abiraterone (Part 2) or ZEN003694 alone, or if unable to do so, as attributable to the combination of enzalutamide (Part 1) or abiraterone (Part 2) and ZEN003694.

Dose escalation will continue after all patients enrolled within a cohort have completed the 28-day Cycle 1 DLT observation period with either 0 of 3 patients, or no more than 1 out of 6 patients in a cohort experiencing a DLT, with the proviso that dose escalation to MTD may be waived in Part 2. Dose escalation decisions will be made based on clinical safety and (when available) PK data (maximum or peak concentration [C_{max}] and AUC) after review by the Cohort Review Committee (CRC), consisting of all Investigators and the Zenith Medical Monitor. If a DLT is observed in 1 of 3 patients in a cohort and confirmed by the CRC, 3 additional patients will be enrolled into that cohort. If 1 of 6 patients in a cohort experiences a DLT, then dose escalation may continue in the next cohort or the MTD of the combination can be declared. If $\geq$ 2 of 3 – 6 patients experience DLTs within a cohort, then the MTD will be considered to have been exceeded and further dose escalation will cease. In this case, if fewer than 6 patients have been enrolled at the previous dose level, that cohort will be expanded to 6 patients to confirm the MTD. Should the MTD of the combination be exceeded at Dose Level 1, a cohort may be explored with a reduced dose of ZEN003694 or enzalutamide (Part 1) or abiraterone (Part 2) at the discretion of the CRC. Cohort management is summarized in **Table 3**.

Table 3: Dose-limiting Toxicity and Cohort Management

Number of Patients with Dose-limiting Toxicity	Action
1 of 1	Add 5 more patients
0 of 3	Proceed to next dose level
1 of 3	Add 3 more patients
1 of 6	Proceed to next dose level
$\geq$ 2 of 3 or $\geq$ 2 of 6	Add 3 more patients in the next lower dose level if only 3 patients were treated in the next lower dose. If 6 patients were treated at the next lower dose level and no more than one patient had DLT, then the next lower

	dose is the MTD.

Part 1: Enzalutamide is a strong inducer of CYP3A4. Treatment with enzalutamide reduces the C_{max} and AUC of the sensitive CYP3A4 substrate midazolam approximately 7- and 4-fold, respectively. ZEN003694 is also a CYP3A4 substrate and therefore the levels of ZEN003694 may be substantially lower when administrated to patients treated with enzalutamide due to increased clearance of ZEN003694 compared to ZEN003694 treatment alone. Enrollment in this study with ZEN003694 in combination with enzalutamide will commence with 36 mg as the starting dose for ZEN003694 and 160 mg dose of enzalutamide (or at a lower stable dose for patients in DE-A or DC-A). The dose of enzalutamide will be held constant through Cycle 1 of the Dose Escalation. After Cycle 1, the dose of enzalutamide may be modified for toxicity per the XTANDI® Package Insert. Due to the possible higher clearance of ZEN003694 during co-administration with enzalutamide, higher doses of ZEN003694 may be needed to achieve sufficient ZEN003694 exposure with the combination treatment than with ZEN003694 alone. If enzalutamide dose is reduced at any time after Cycle 1, PK samples are to be obtained 28 Days (±7 Days) following dose modification. Dose escalation of ZEN003694 in this study will proceed as follows in **Table 4** unless intervening toxicity is observed.

Table 4: Part 1 Dose Escalation Scheme

Dose Level	ZEN003694 (mg)	Fold Increase from Prior Dose Level
1	36	--
2	48	1.33
3	60	1.25
4	72	1.20
5	96	1.33*
Additional levels may be explored at the discretion of the CRC		

Part 2: [redacted]Enrollment in this study with ZEN003694 in combination with abiraterone will therefore commence with 72 mg QD as the starting dose for ZEN003694 and 1000 mg dose of abiraterone once. The dose of abiraterone will be held constant at 1000 mg through Cycle 1 of the Dose Escalation. After Cycle 1, the dose of abiraterone may be modified for toxicity per the ZYTIGA® Package Insert. Dose escalation/de-escalation of ZEN003694 in this study will proceed as follows in **Table 5** unless intervening toxicity is observed.

Table 5: Part 2 Dose Escalation Scheme

Dose Level	ZEN003694 (mg) *	Fold Increase from Prior Dose Level
-1	48	0.67
1	72	--
2	96	1.33
* Dose de-escalation from 72 mg is allowed by cohort. Additional dose levels may be explored based on safety and at the discretion of the CRC, with the proviso that dose escalation to MTD may be waived in Part 2.		

Part 1 and Part 2:

Dose escalation increments between cohorts will be determined by the CRC based on safety and available PK data (e.g., C_{max} and AUC) based on the following schema:

- Dose escalation up to 2-fold is allowed in Dose Level 2 and 3 unless one drug-related Grade 2 event is observed in Dose Level 1 and 2, respectively
- Subsequent dose escalation up to 1.5-fold is allowed until a DLT is observed
- Subsequent dose escalation up to 1.33-fold is allowed until MTD is established, or, in Part 2, if MTD is waived and RP2D is declared

All dose escalations will be guided by the available PK data (e.g., C_{max} and AUC) from both **ZEN003694-001** and this study, ZEN003694-002, with respect to the combined AUC_{0-24} of ZEN003694 and its active metabolite ZEN003791. [redacted]

Intermediate doses and/or alternative dosing schedules may be evaluated to best determine the MTD and/or RP2D of ZEN003694 in combination with enzalutamide (Part 1) or abiraterone (Part 2) based on evaluation of clinical safety and available PK data (e.g., C_{max} and AUC) and upon agreement of the CRC members. No intra-patient dose escalation is allowed during the first three cycles of therapy. If a patient has not experienced any Grade 2 or higher drug-related AEs after three cycles, dose escalation up to the highest dose currently declared tolerable by the CRC will be allowed and further intra-patient dose escalation(s) will be determined on a cycle-by-cycle basis at the discretion of the Investigator and with approval from the CRC.

5.1.2 Definition of Dose-limiting Toxicity

Determination of DLT will be made during the first 28 days of treatment (i.e., Cycle 1) in the dose escalation phase. Toxicity will be graded and recorded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03 (see **Appendix 2**). A DLT is defined as a clinically significant AE or laboratory abnormality that is

considered possibly, probably or definitely related to ZEN003694 and which meets any of the following criteria:

- Grade 3 or greater non-hematologic clinical toxicity with the exception of Grade 3 nausea or Grade 3/4 vomiting and diarrhea persisting less than 72 hours in the absence of maximal medical therapy
- Grade 4 neutropenia lasting more than 5 days
- Grade 3 or greater febrile neutropenia (temperature ≥ 38.5ºC)
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with clinically significant bleeding, or any requirement for platelet transfusion
- Any other Grade 3 or 4 laboratory abnormality that requires hospitalization
- An ALT > 3x ULN with concomitant total bilirubin > 2x ULN
- Any ZEN003694-related toxicity that results in more than 25% of missed doses during Cycle 1 of treatment
- In the situation where toxicity requires withholding ZEN003694 following the receipt of at least 75% of scheduled dosing during Cycle 1: Failure to begin Cycle 2 within 1 week of the scheduled start date due to ongoing toxicity

All patients experiencing a DLT must discontinue dosing with ZEN003694; patients must complete the Safety Follow-up visit prior to discontinuation from the study.

Determination of evaluability will be made during the first 28 days of ZEN003694 treatment (i.e., Cycle 1) in the dose escalation phase. Patients meeting one or more of the following will be considered unevaluable and will be replaced:

- Patients who miss more than 25% of ZEN003694 and/or enzalutamide or abiraterone doses or fail to begin Cycle 2 within 1 week of the scheduled start date for reasons other than ZEN003694-related toxicity
- Patients who require enzalutamide or abiraterone dose hold or modification in Cycle 1, including during the 14-day Lead-in period for reasons other than ZEN003694-related toxicity
- **Part 1 only**: If a patient is unable to tolerate enzalutamide for any reason at dose of 160 mg during the 14 day Lead-in prior to first dose of ZEN003694, then the patient should not receive ZEN003694, and be withdrawn from the study and replaced
- **Part 2 only:** If a patient is unable to tolerate for any reason abiraterone at dose of 1000 mg once daily during the 14 day Lead-in prior to first dose of ZEN003694, then the patient should not receive ZEN003694, and be withdrawn from the study and replaced

5.1.3 Definition of the Maximum Tolerated Dose

The MTD is defined as the highest dose level of ZEN003694 in combination with enzalutamide (Part 1) and abiraterone (Part 2; if MTD is determined) at which no more than 1 of 6 patients experiences a DLT during the first cycle of therapy. MTD may be declared independently for any given dosing regimen, i.e., the respective MTDs for once daily dosing, twice daily dosing, and any alternative dosing regimen(s) need not be at the same dose.

5.1.4 Definition of the Recommended Phase 2 Dose

The RP2D is defined as the dose level of ZEN003694 in combination with enzalutamide (Part 1) and abiraterone (Part 2) recommended for further clinical study. In Part of this study the RP2D may be the same as the MTD or modified from the MTD based on assessments of overall exposure, safety experience in Cycle 2 and beyond, PD and clinical benefit data. In Part 2 of this study the determination of an MTD may be waived and the RP2D may be declared based on assessment of overall exposure, safety experience , PD and clinical benefit data. The RP2D of ZEN003694 in combination with enzalutamide (Part 1) or abiraterone (Part 2) will be determined in the dose confirmation phase of the study. RP2D may be declared independently for any given Part or dosing regimen, i.e., the respective RP2Ds for once daily dosing, twice daily dosing, and any alternative dosing regimen(s) need not be at the same dose.

5.1.5 Dose Confirmation

Part 1, ZEN003694 in combination with enzalutamide: Once the MTD of ZEN003694 in combination with enzalutamide has been determined in the dose escalation portion of Part 1 of the study, up to 20 patients who meet the inclusion/exclusion criteria for Cohort A and up to 20 patients who meet the inclusion/exclusion criteria for Cohort B of the dose confirmation phase will be enrolled for further evaluation of safety, PK, PD and preliminary clinical activity.

Enzalutamide-naïve and apalutamide-naïve patients in Cohort DC-B will be administered enzalutamide (160 mg) orally once daily for 14 days prior to the initiation of the combination therapy (Lead-in) to reach enzalutamide C_{ss} during Cycle 1. After the Lead-in, ZEN003694 will be administered orally in combination with daily enzalutamide for 28-day cycles. Patients in Cohort DC-A who are currently receiving a stable dose of enzalutamide will continue to receive enzalutamide and will not participate in the Lead-in. Patients in Cohort DC-A who are not currently receiving enzalutamide or apalutamide or are currently taking apalutamide will be administered enzalutamide orally once daily for 14 days prior to the initiation of the combination therapy (Lead-in) to reach enzalutamide C_{ss} during Cycle 1. After the Lead-in, ZEN003694 will be administered orally in combination with daily enzalutamide for 28-day cycles.

Part 2, ZEN003694 in combination with abiraterone: Once the CRC has determined a recommended phase 2 dose (RP2D) of ZEN003694 in combination with abiraterone in the dose escalation portion of Part 2 of the study, up to 20 patients who meet the inclusion/exclusion criteria for Cohort DC-C and up to 20 patients who meet the inclusion/exclusion criteria for

Cohort DC-D of the dose confirmation phase will be enrolled for further evaluation of safety, PK, PD and preliminary clinical activity.

- Cohort DC-D: Abiraterone-naïve patients in Cohort DC-D will be administered abiraterone (1000 mg once daily) orally for 14 days prior to the initiation of the combination therapy (Lead-in) to reach abiraterone C_{ss} during Cycle 1. After the Lead-in, ZEN003694 will be administered orally in combination with daily for 28-day cycles.
- Cohort DC-C: Patients in Cohort DC-C are currently receiving a stable dose of abiraterone (as part of the study entry criteria for this cohort) and will continue to receive abiraterone when enrolled in the dose confirmation phase of the study and will not participate in the Lead-in.

Part 1 and Part 2: When the 6th patient in each cohort in the dose confirmation phase has completed one cycle of therapy, or earlier if clinically indicated, the CRC will review the safety data. If ≥ 2 patients have experienced drug-related SAEs or DLT-equivalent events, the CRC may recommend a modification in the dose or regimen of ZEN003694 in combination with enzalutamide (Part 1) or abiraterone (Part 2) for the dose confirmation phase.

5.2 Safety Review

Safety will be assessed by periodic physical examinations, weight, ECOG performance status, vital signs, clinical laboratory assessments including serum troponin, 12-lead electrocardiogram (ECG) and monitoring of AEs (see Schedule of Events **Table 1** & **Table 2**). AEs will be graded using NCI CTCAE Version 4.03 (see **Appendix 2**). Teleconferences with members of the CRC will be held during the dose escalation phase to discuss any suspected DLTs that have occurred in patients within each cohort. The frequency of the teleconference calls will be determined by the rate of enrollment, data review, frequency of DLT notifications, discussions with investigational sites and other factors. Approximately one week after the last patient in a dose cohort completes Cycle 1 and prior to escalating to the next dose level (or de-escalating), the CRC will review toxicities and available PK (e.g., C_{max} and AUC) from the current cohort of the study during a teleconference.

The CRC‘s responsibilities during the course of the study include:

- Review all relevant safety findings and confirm all DLTs
- Review and approve all intra-patient dose escalation(s)
- Determine all cohort dose escalation and de-escalation decisions during the dose escalation phase
- Recommend alternative dose and regimen as appropriate

- Determine the MTD and RP2D; and, in Part 2, determine whether MTD should be determined or, alternatively, that the RP2D may be declared without establishing MTD per the protocol definition (Section 5.1.3)
- Recommend the dose(s) and regimen(s) to extend into the dose confirmation phase
- Consider any relevant safety data from Study **ZEN003694-001**
- Further monitor safety during the dose confirmation phase, including review of the safety data after the sixth patient completes Cycle 1

5.3 Number of Sites and Patients

Part 1: Up to 80 evaluable patients will be enrolled in the study at up to 10 sites in the United States. Approximately 40 patients will be enrolled in the dose escalation phase and up to 40 patients will be enrolled in the dose confirmation phase.

Part 2: Up to 55 evaluable patients will be enrolled in the study at up to 10 sites in the United States. Approximately 15 patients will be enrolled in the dose escalation phase and up to 40 patients will be enrolled in the dose confirmation phase.

5.4 Study Duration

The study duration by Part including the enrollment period and follow-up for both the dose escalation and dose confirmation phases is approximately 36 months, depending upon total enrollment. Patients may continue receiving ZEN003694 in combination with enzalutamide (Part 1) or abiraterone (Part 2) until disease progression by PCWG2 criteria, unacceptable toxicity, requirement for non-protocol therapy or patient withdrawal from study. Patients with PSA-only progression may remain on study until clinical and/or radiographic evidence of progression by PCWG2 criteria.

5.5 Premature Study Termination or Suspension of Enrollment

Zenith has the right to terminate the participation of an individual study site, study Part, or the entire study, at any time, for any reason. Reasons for terminating the study include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory
- Data records are inaccurate or incomplete
- The Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting the study

- A decision on the part of Zenith to suspend or discontinue testing, evaluation or development of ZEN003694

In addition, Zenith may suspend enrollment in the study at any time for any reason.

All Investigators and appropriate Regulatory Authorities will be promptly notified upon early termination of the study. In addition, Investigators and Regulatory Authorities will be promptly notified if enrollment is terminated or suspended for any reason.

6. STUDY DRUG AND CONCOMITANT TREATMENT

6.1 ZEN003694

ZEN003694 is a novel, potent BET inhibitor currently under clinical investigation. It is provided in two dosage strengths: 12 mg and 48 mg. ZEN003694 will be administered orally in 28-day cycles and should be ingested with a full (8-ounce) glass of water at least 1 hour before eating or 2 hours after eating (fasting). Each capsule should be swallowed whole. Patients should be advised not to chew, dissolve, or open the capsules. Patients should also be advised to minimize their exposure to sunlight.

6.2 Enzalutamide

Enzalutamide is an androgen receptor inhibitor indicated for the treatment of patients with mCRPC. Enzalutamide 160 mg (four 40 mg capsules) will be administered orally once daily according to the XTANDI® Package Insert without food in 28-day cycles through Cycle 1 in Dose Escalation for all enzalutamide-naïve patients (DE-B and DC-B cohorts). For patients in DE-A and DC-A cohorts, enzalutamide will be administered at the dose level previously determined to be stable and that has not changed for at least two weeks prior to starting Cycle 1 Day 1 combination study treatment or restarting enzalutamide treatment in the Lead-in phase. After Cycle 1 of Dose Escalation or any time in Dose Confirmation, the dose of enzalutamide may be modified for toxicity per the XTANDI® Package Insert. Each capsule should be swallowed whole. Patients should be advised not to chew, dissolve, or open the capsules.

6.3 Abiraterone

Abiraterone is an androgen synthesis inhibitor indicated for the treatment of patients with mCRPC. Abiraterone 1000 mg (four 250 mg capsules) will be administered orally once daily according to the ZYTIGA® Package Insert without food in 28-day cycles. Prednisone 5 mg (one 5 mg capsule) will be administered orally twice daily in 28-day cycles. In Dose Escalation, the dose of abiraterone will be held constant at 1000 mg throughout Cycle 1 of the study. After Cycle 1, the dose of abiraterone may be modified for toxicity per the ZYTIGA® Package Insert.

6.4 Guidelines for Dose Escalation, Dose Modification and Management of ZEN003694-related Toxicity

6.4.1 Dose Escalation in the Dose Escalation Phase of the Study

No intra-patient dose escalation is allowed during the first three cycles of treatment. If a patient has not experienced any Grade 2 or higher drug-related AEs after three cycles, dose escalation up to the highest dose currently declared tolerable by the CRC will be allowed and further intra-patient dose escalation(s) will be determined on a cycle-by-cycle basis at the discretion of the Investigator and with approval from the CRC. Patients who required a dose reduction due to toxicity at any time will not be allowed to re-escalate to a higher dose level.

6.4.2 Management of ZEN003694-related Toxicity in the Dose Escalation and Dose Confirmation Phases

Dose adjustment (hold or reduction) of ZEN003694 is allowed in the dose escalation phase of the study beyond Cycle 1 and will be based on the toxicities that are deemed possibly, probably or definitely related to ZEN003694. Dose reductions of ZEN003694 during Cycle 1 will not be allowed however ZEN003694 doses may be held due to treatment-related toxicity. If ZEN003694 treatment is withheld for toxicity attributed by the Investigator to ZEN003694 alone, then enzalutamide dosing may continue unmodified. For guidance regarding what ZEN003694-related toxicities qualify as a DLT in Cycle 1 of the dose escalation phase of the study, refer to Section **5.1.2** Definition of Dose Limiting Toxicity.

Dose adjustment (hold or reduction) of ZEN003694 is allowed in the dose confirmation phase of the study at any time and will be based on the toxicities that are deemed possibly, probably or definitely related to ZEN003694. If ZEN003694 treatment is withheld for toxicity attributed by the Investigator to ZEN003694 alone, then enzalutamide dosing may continue unmodified.

Dose adjustment and toxicity management guidelines are summarized in **Table 6**.

Table 6: ZEN003694-Related Dose Adjustment and Toxicity Management Guidelines

Event	Hematologic & Non-hematologic Toxicity (Excluding Anemia)
Grade 1	No change
Grade 2	No change required; but a dose hold for Grade 2 laboratory toxicity or a laboratory trend of concern is allowed based on Investigator discretion. In cases where the dose is held, if toxicity or trend is reduced to a Grade 1 within 14 days, treatment may resume at a dose level and regimen determined by mutual agreement between the Investigator and Zenith.
Grade 3	Hold treatment. If toxicity resolves to baseline or Grade 1 within 14 days, treatment may resume at the same dose level. If toxicity is reduced to Grade 2 within 14 days, treatment may resume at one dose level below or at a reduced frequency (except in Cycle 1 of dose escalation) with mutual agreement between the Investigator and Zenith.
Grade 4	Hold treatment. If toxicity is resolved to Grade ≤ 2 within 14 days, treatment may resume at one dose level below or at a reduced frequency (except in Cycle 1 of dose escalation) with mutual agreement between the Investigator and Zenith.

Dose interruption caused by any ZEN003694-related toxicities lasting longer than 14 days (hematologic or non-hematologic toxicity) will result in study drug discontinuation unless there is objective evidence of benefit. Any subject experiencing concomitant ALT elevation to > 3x ULN and bilirubin elevation to > 2x ULN will be permanently discontinued from dosing with ZEN003694.

Only one re-challenge at the same dose level is allowed and two dose reductions and/or decrease in dosing frequency is allowed.

6.5 Part 1: Management of Enzalutamide-related Toxicity in the Dose Escalation and Dose Confirmation Phases

No dose adjustment (hold or reduction) of enzalutamide is allowed during Cycle 1 in the dose escalation phase of the study. For toxicities in dose escalation Cycle 1 that, in the opinion of the investigator, could reasonably be attributed to either study drug (eg, fatigue, nausea), the investigator should hold ZEN003694 first as a "therapeutic trial", and only hold enzalutamide in addition if the trial hold of ZEN003694 is unsuccessful in managing toxicity. Holding enzalutamide in dose escalation Cycle 1 will render the subject unevaluable for DLT determination (**5.1.2** Definition of Dose Limiting Toxicity), although the subject may continue in the trial if recommended by the investigator and approved by Zenith.

If a patient in Dose Escalation or Dose Confirmation Cohort B is unable to tolerate enzalutamide for any reason at dose of 160 mg during the 14 day Lead-in prior to first dose of ZEN003694, then the patient should not receive ZEN003694, and be withdrawn from the study and replaced.

Beyond Cycle 1 in the dose escalation phase and any time during the dose confirmation phase, enzalutamide toxicity may be managed per the XTANDI® Package Insert. In the case that enzalutamide is held to manage enzalutamide-related toxicity, the Investigator should contact Zenith to discuss possible dose adjustment or hold of ZEN003694. If enzalutamide is held greater than 14 days the subject must withdraw from the study unless he is, in the Investigator's judgment, clearly benefitting from ZEN003694 treatment alone, in which case the Investigator must consult with Zenith regarding continuing ZEN003694 monotherapy with possible modification of the dose. If enzalutamide dose is reduced at any time after Cycle 1 in Dose Escalation or any time in Dose Confirmation, PK samples are to be obtained 28 Days (±7 Days) following dose modification at the following time-points: pre-ZEN003964 and enzalutamide doses, and 15 minutes (±5 min), 30 min (±5 min), 1 hour (±5 min), 2 hours (±10 min), 4 hours (±15 min), 6 hours (±15 min) and 8 hours (±30 min) post-ZEN003694 and enzalutamide doses.

Commonly reported adverse reactions with enzalutamide include asthenia/fatigue, back pain, decrease appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension and dizziness/vertigo. In patients who have previously received docetaxel treatment, neutropenia and infections have been reported. Falls and hypertension have also been reported. Management of enzalutamide side effects are at the discretion of the Investigator. Refer to XTANDI® Package Insert in **Appendix 4** for further information.

Warning and precautions with enzalutamide include:

- Seizures in patients with mCRPC who previously received docetaxel.
- Posterior reversible encephalopathy syndrome (PRES) in post approval reports. PRES diagnosis should be confirmed by brain imaging and enzalutamide should be

discontinued. Symptoms present as seizures, headache, lethargy, confusion, blindness and other visual and neurological disturbances, with or without associated hypertension.

Patients who experience seizures or PRES must discontinue the study.

6.6 Part 2: Management of Abiraterone-related Toxicity in the Dose Escalation and Dose Confirmation Phases

No dose adjustment (hold or reduction) of abiraterone is allowed during Cycle 1 in the dose escalation phase of the study. For toxicities in dose escalation Cycle 1 where, in the opinion of the investigator, the attribuation to one drug or the other is unclear, the investigator should hold ZEN003694 first as a "therapeutic trial", and only hold abiraterone in addition if the trial hold of ZEN003694 is unsuccessful in managing toxicity. Holding abiraterone in dose escalation Cycle 1 will render the subject unevaluable for DLT determination (**5.1.2** Definition of Dose Limiting Toxicity), although the subject may continue in the trial if recommended by the investigator and approved by Zenith.

If a patient in Dose Escalation or Dose Confirmation Cohort D is unable to tolerate abiraterone for any reason at dose of 1000 mg during the 14 day Lead-in prior to first dose of ZEN003694, then the patient should not receive ZEN003694, and be withdrawn from the study and replaced.

Beyond Cycle 1 in the dose escalation phase and any time during the dose confirmation phase, enzalutamide toxicity may be managed per the ZYTIGA® Package Insert.

The most common adverse drug reactions (≥5%) reported in clinical studies were joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, and upper respiratory tract infection. The most common adverse drug reactions that resulted in drug discontinuation were aspartate aminotransferase increased, alanine aminotransferase increased, urosepsis and cardiac failure (each in <1% of patients taking ZYTIGA). Management of abiraterone side effects are at the discretion of the Investigator. Refer to ZYTIGA® Package Insert in **Appendix 5** for further information.

Warning and precautions with abiraterone include:

- Hypertension, hypokalemia, and fluid retention due to mineralocorticoid excess
- Adrenocortical insufficiency
- Hepatotoxicity

6.7 Treatment Compliance

Trained study personnel will dispense ZEN003694 and will instruct the patients on drug administration at least 1 hour before eating or 2 hours after eating (fasting). Treatment compliance will be monitored by the review of the patient's dosing diary and drug accountability records. Study treatment administration data will be recorded in the patient's medical record and on the Drug Administration electronic case report forms (eCRFs).

6.8 Concomitant Medications and Therapies

6.8.1 Part 1 and Part 2: Prohibited Concomitant Medications and Therapies with ZEN003694

ZEN003694 is primarily metabolized by CYP3A4. Therefore, strong inhibitors and inducers of CYP3A4 (except enzalutamide) must be excluded during ZEN003694 administration. [redacted]

Because of the known risk of QT/QTc prolongation from 5-hydroxytryptamine type 3 (5-HT3) receptor anti-emetics, 5-HT3 receptor antagonist antiemetic drugs should be used with Investigator discretion, if alternative drugs are not available. Dolasetron should be avoided, as the prolongation of QTc may be greater with this drug based upon American Society of Clinical Oncology (ASCO) guidelines (**Basch et al., 2011**). To date, ZEN003694 has shown no evidence of QT prolongation, suggesting that drugs such as 5-HT3 antagonists may be safely used concomitantly where indicated by the Investigator's clinical judgment.

During the study, other chemotherapy, immunotherapy, radiation (except, if ≤ 5 fractions for palliative care of solitary bone lesions), bone-targeting radionuclides, or surgery is also prohibited. Therapeutic anticoagulation with warfarin, apixaban, or other anti-factor agents is not permitted, but low-dose warfarin for maintenance of port patency or prophylactic anti-platelet agents are allowed.

6.8.2 Part 1: Prohibited Concomitant Medications and Therapies with Enzalutamide

Enzalutamide is a substrate of CYP2C8 and therefore use of strong CYP2C8 inhibitors should be avoided because CYP2C8 inhibitors increase the plasma exposure of enzalutamide.

Enzalutamide is also a moderate inducer of CYP2C9 and CYP2C19; thus enzalutamide may decrease plasma exposures of these drugs that are significant substrates of these enzymes.

Refer to XTANDI® (enzalutamide) Package Insert in **Appendix 4** for further information regarding potential drug-drug interactions.

Enzalutamide is a strong inducer of CYP3A4, and thus may alter the kinetics of ZEN003694.

Use of moderate CYP3A4 inhibitors and inducers, significant CYP1A2 substrates, CYP2C8 inhibitors, or significant CYP3A4, CYP2C9 and CYP2C19 substrates will be determined on a case-by-case basis at the discretion of the Investigator and with approval from Zenith.

A list of inhibitors, inducers and substrates are listed in **Table 7**. This list is not comprehensive; when considering use of a medication that could be a potential CYP3A4 inhibitor or inducer, CYP1A2 substrate, CYP2C8 inhibitor or significant CYP3A4, CYP2C9 or CYP2C19 substrate, the Investigator should consult with Zenith.

Table 7: Part 1 Inhibitors and Inducers of Relevant Drug-metabolizing Enzymes

Category	Inhibitors of CYP3A4 (May increase ZEN003694 exposure)	Inducers of CYP3A4 (May decrease ZEN003694 exposure)	Substrates of CYP1A2 [redacted]
AVOID	boceprevir clarithromycin conivaptan grapefruit juice indinavir itraconazole ketoconazole lopinavir/ritonavir mibefradil nefazodone nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin voriconazole	avasimibe rifampin St. John's wort	ramelteon tizanidine theophylline

Source: http://www fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664 htm

Sites are to consider the following potential drug interactions when enrolling patients:

- [redacted]
- Gemfibrozil inhibits CYP2C8 and may increase exposure to enzalutamide

- The following are substrates of CYP3A4/CYP2C9/CYP2C19 and exposure to these drugs may be decreased by enzalutamide:
    - CYP3A4: alfentanil, astemizole, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, Cannabidiol (CBD) enriched products, midazolam, triazolam, lovastatin, simvastatin
    - CYP2C9: warfarin, phenytoin, celecoxib
    - CYP2C19: S-mephenytoin

Any CYP3A4 inhibitors, inducers and substrates, CYP2C8 inhibitors, and CYP3A4, CYP1A2, CYP2C9 and CYP2C19 substrates taken by the patient during the study period must be documented in the patient's chart and on the Concomitant Medications eCRF. If Zenith's approval is not obtained prior to administration of these medications, the patient may be withdrawn from the study by Zenith.

6.8.3 Part 2: Prohibited Concomitant Medications and Therapies with Abiraterone

Abiraterone is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the Cmax and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily. Avoid coadministration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine).

Abiraterone is a substrate of CYP3A4, but in vivo the strong CYP3A4 inhibitor ketoconazole had no clinically meaningful impact on abiraterone exposure. The strong CYP3A4 inducer rifampicin decreased abiraterone exposure by half. Hence, strong CYP3A4 inducers should be avoided or used with caution as they may diminish the effectiveness of abiraterone.

A list of inhibitors, inducers and substrates are listed in **Table 8**. This list is not comprehensive; when considering use of a medication the Investigator should consult with Zenith.

Table 8: Part 2 Inhibitors and Inducers of Relevant Drug-metabolizing Enzymes

Category	Inhibitors of CYP3A4 (May increase ZEN003694 exposure)	Inducers of CYP3A4 (May decrease abiraterone and/or ZEN003694 exposure)	Substrates of CYP2D6 (exposure may be increased by abiraterone)	Substrates of CYP1A2 [redacted]
AVOID	boceprevir clarithromycin conivaptan grapefruit juice indinavir itraconazole ketoconazole lopinavir/ritonavir mibefradil nefazodone nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin voriconazole	avasimibe rifampin St. John's wort	thioridazine	ramelteon tizanidine theophylline

Source: http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664 htm

Any CYP3A4 inhibitors, inducers and substrates, CYP1A2 and CYP2D6 substrates taken by the patient during the study period must be documented in the patient's chart and on the Concomitant Medications eCRF. If Zenith's approval is not obtained prior to administration of these medications, the patient may be withdrawn from the study by Zenith.

6.8.4 Permitted Concomitant Medications and Therapies

Use of corticosteroids is allowed up to a daily dose of 10 mg prednisone or equivalent provided that the dose has been stable for at least 2 weeks prior to the start of ZEN003694 dosing and will remain stable during ZEN003694 treatment.

Unlike the reported experience with other BET Inhibitors, ZEN003694 treatment has not been associated with clinically important thrombocytopenia in the 75 patients treated with ZEN003694 to date. Therefore, the prophylactic use of anti-platelet agents (eg, low-dose aspirin, clodiprogel) is permitted but should be carefully reassessed in any patient in whom thrombocytopenia occurs.

Treatment with antiemetic therapy will be permitted, if clinically indicated. Based on experience, Investigators are encouraged to instruct their patients to take anti-emetics and maintain adequate hydration at first signs of GI intolerance. Patients should be provided 'filled' prescriptions for an anti-emetic, if possible, or ensure patients fill their prescriptions of an anti-emetic on the first day of dosing (C1D1). Patients are to be instructed to take the anti-emetic at first signs of nausea.

Treatment with filgrastim or other colony stimulating factors will be permitted for Grade 3 or higher hematologic toxicity as per Package Insert, but may not be used prophylactically. Patients should receive full supportive care, including hematopoietic growth factors based upon ASCO guidelines (**Smith et al., 2015**), if clinically indicated.

Treatment required for care of complications/adverse events arising from the cancer and/or treatment will be permitted.

All concomitant medications must be recorded on the Concomitant Medications eCRF.

7. STUDY DRUG AND MATERIALS

7.1 Study Drug Description

7.1.1 Formulation

ZEN003694 capsules for oral administration are supplied as 12 mg and 48 mg capsules containing ZEN003694 as the active substance with no additional excipients filled in the capsule. The 12 mg ZEN003694 capsules are size 3, Swedish orange, hard gelatin capsules and the 48 mg ZEN003694 capsules are size 0, white opaque, hard gelatin capsules.

The drug substance is manufactured under Good Manufacturing Practice conditions by [redacted]. The drug product is manufactured, packaged and labeled by [redacted] Capsules are packaged in high density polyethylene opaque, white resin bottles with screw-cap, child-resistant closures.

7.1.2 Storage Conditions

Study product should be securely stored at room temperature 20° – 25°C (68° – 77°F) (excursions from 15° – 30°C [59° – 86°F] are permitted). Protect from light and do not freeze.

7.2 Enzalutamide

See XTANDI®Package Insert (**Appendix 4**) for detailed information on enzalutamide description, formulation and storage conditions.

7.3 Abiraterone

See ZYTIGA® Package Insert (**Appendix 5**) for detailed information on abiraterone description, formulation, and storage conditions.

7.4 Study Drug Accountability

The Investigator, pharmacist or qualified designee is responsible for making an inventory of study drug upon receipt. All used and unused study drug must be retained until final reconciliation or as indicated by Zenith. The study drug is to be administered/dispensed by the Investigator or appropriately qualified site personnel named on the delegation of authority log. Under no circumstances will the Investigator allow the study drug to be used other than as directed by this protocol. Although appropriate personnel may be designated to administer/dispense drug and maintain drug accountability records, the Investigator is ultimately responsible for all drug accountability.

The Investigator or designee must maintain accurate records of the receipt, disposition and return of study drug. Documentation of drug disposition/return should identify the patient receiving the study drug, the quantities (by dosage strength) of study drug dispensed/returned and dates study drug were dispensed/returned/destroyed. This documentation is required in addition to drug accountability information recorded on eCRFs. A copy of the reconciled drug inventory record will be provided to Zenith or its designee, and the study site will retain the original record. A written explanation must be provided for any discrepancies.

Zenith representatives will authorize the return or destruction of all used, partially used, and unused bottles of study drug. If the study site is capable of destroying study drug it may do so upon authorization by Zenith. Records will include date of destruction or return, and quantities destroyed or returned to Zenith or its designee. Detailed instructions on study drug accountability will be provided in a study reference manual.

Part 1 only: Enzalutamide will be used by patients as Standard of Care. Patients will record their daily administration of enzalutamide in an Enzalutamide Dosing Diary. Enzalutamide Dosing Diaries will be reviewed for subject compliance by appropriate site staff. Detailed instructions regarding enzalutamide compliance will be provided in a study reference manual.

Part 2 Only: Abiraterone will be used by patients as Standard of Care. Patients will record their daily administration of abiraterone in an Abiraterone Dosing Diary. Abiraterone Dosing Diaries will be reviewed for subject compliance by appropriate site staff. Detailed instructions regarding abiraterone compliance will be provided in a study reference manual. Prednisone will be documented as a concomitant medication on the applicable log in patient source documentation.

8. STUDY PROCEDURES AND ASSESSMENTS

The Schedule of Events (**Table 1** & **Table 2**) is given as an aid to patient management. This section describes evaluations to be performed before, during and after treatment. Scheduled clinic attendance should occur within ± 3 days of the specified dates at all visits. Where this is not possible because of extenuating circumstances (e.g., holidays, vacations), the reason should be noted in the patient's chart.

All AEs that occur anytime during the study and any concomitant medication use should be recorded on the CRFs. Patients with Grade 2, 3 or 4 study drug-related toxicity should be followed as the Investigator deems clinically appropriate. The duration and time to resolution of AEs should be evaluated and recorded in the patient's chart and on the AE eCRF. Additional evaluations may be performed as necessary.

8.1 Study Procedures by Visit

8.1.1 Screening Visit

All screening tests must be performed within 28 days before the first day of treatment (Cycle 1, Day -14 if enzalutamide or abiraterone Lead-in is required). The informed consent form (ICF) must be signed before screening procedures are performed (see Section **8.2.1**).

Screening will include:

- Collection of information on status of inclusion and exclusion criteria (see Section **8.2.2**)
- Complete medical history, including cancer history, prior PSA data, prior cancer-related surgery and treatments, and demographic history (see Section **8.2.3**)
- Listing of all medications taken within 21 days of enrollment and any ongoing medications
- Physical examination including height (cm) and weight (kg) (see Sections **8.2.4** and **8.2.5**)
- ECOG performance status (see Section **8.2.6** and **Appendix 1**)
- Vital signs (temperature [Fº], blood pressure and heart rate) (see Section **8.2.7**)
- Hematology (see Section **8.2.8**)
- Coagulation tests (see Section **8.2.8**)
- Serum chemistries (see Section **8.2.8**): including serum testosterone
- PSA

- Urinalysis (see Section **8.2.8**)
- Echocardiogram or multigated acquisition (MUGA) scan (see Section **8.2.9**)
- Triplicate 12-lead ECG (see Section **8.2.10**)
- Ophthalmology assessments (see Section **8.2.16)** To be performed prior to first dose of ZEN003694 and after all entry criteria have been satisfied and enrollment is approved
- Part 1 Only: Qualitative Exploration of Visual Symptoms (see Section **8.2.16)**
- PD samples: whole blood for exploratory immuno-oncology biomarkers (Only in **Part 1, DE Only**) (at selected clinical sites only; see Section **8.2.12**): (Prior to the Day -14 Lead-in for patients requiring enzalutamide Lead-in (Part 1))
- Fresh tumor biopsy samples (optional during dose escalation phase, mandatory during dose confirmation phase). For those patients in DE-A or DC-A (Part 1) or DE-C or DC-C (Part 2) who are not currently taking enzalutamide (Part 1) or abiraterone (Part 2) and require the 14 day Lead-in, the screening fresh tumor biopsy samples can be collected from time of consent through Cycle 1 Day -1, preferably during the 14 day enzalutamide (Part 1) or abiraterone (Part 2) Lead-in. (see Section **8.2.12**)
- Tumor assessment (see Section **8.2.15**) Imaging for tumor assessments may be scheduled up to 7 days prior to the scheduled clinic visit day.

8.1.2 Cycle 1 Lead-in for Dose Escalation & Dose Confirmation (required for Cohorts DE-B, DC-B, DE-D, DC-D; also required for patients requiring enzalutamide Lead-in (Part 1: Sub-arm A2) or abiraterone Lead-in (Part 2: Sub-arm C2)

Day -14 (-14 days ± 1 day from Cycle 1 Day 1) (Pre-enzalutamide Dose (Part 1) / Pre-abiraterone dose (Part 2))

- Hematology (if Screening visit tests were performed more than 7 days prior to this visit)
- Coagulation tests (if Screening visit tests were performed more than 7 days prior to this visit)
- Serum chemistries tests (if Screening visit tests were performed more than 7 days prior to this visit)
- Urinalysis (if Screening visit tests were performed more than 7 days prior to this visit)
- PSA tests (if Screening visit tests were performed more than 7 days prior to this visit)
- Qualitative Exploration of Visual Symptoms (see Section **8.2.16)**

- PD samples: whole blood for CTCs for enumeration and PD (**DE and DC**), and plasma for exploratory PD (**DC only)** (see Section **8.2.12**)
- PD samples: whole blood for exploratory cfDNA and ctDNA (For all patients requiring enzalutamide Lead-in **(Part 1: DE-B and DC-B and DE-A and DC-A Sub-arm A2)** & for all patients requiring abiraterone Lead-in **(Part 2: DE-D and DC-D and DE-C and DC-C Sub-arm C2**)

Day -14 (Enzalutamide (Part 1) or Abiraterone (Part 2) Dosing)

- Part 1: Enzalutamide daily at least 1 hour before eating or 2 hours after eating
- Part 2: Abiraterone once daily at least 1 hour before eating or 2 hours after eating

Day -14 (Post-enzalutamide Dose (Part 1) or Post-abiraterone Dose (Part 2))

- AEs (see Section **8.2.13**)
- Concomitant medications (see Section **8.2.14**)

8.1.3 Cycle 1 Dose Escalation and Dose Confirmation

Day 1 (Pre-dose)

- Symptom-directed physical examination and weight
- ECOG performance status
- Vital signs (temperature [Fº], blood pressure and heart rate)
- Hematology (Collect for all patients requiring Cycle 1 Lead-in. For patients who do not require Cycle 1 Lead-in, collect if Screening visit tests were performed more than 7 days prior to this visit)
- Coagulation tests (Collect for all patients requiring Cycle 1 Lead-in. For patients who do not require Cycle 1 Lead-in, collect if Screening visit tests were performed more than 7 days prior to this visit)
- Serum chemistries including serum testosterone (Collect for all patients requiring Cycle 1 Lead-in. For patients who do not require Cycle 1 Lead-in, collect if Screening visit tests were performed more than 7 days prior to this visit)
- Serum troponin level
- PSA (Collect for all patients requiring Cycle 1 Lead-in. For patients who do not require Cycle 1 Lead-in, collect if Screening visit tests were performed more than 7 days prior to this visit)

- Urinalysis (Collect for all patients requiring Cycle 1 Lead-in. For patients who do not require Cycle 1 Lead-in, collect if Screening visit tests were performed more than 7 days prior to this visit)
- Triplicate 12-lead ECG
- PK sample for ZEN003694 and enzalutamide (Part 1) or abiraterone (Part 2) (see Section **8.2.11**)
- PD samples: whole blood for BET inhibitor gene expression profile (**DE and DC**), exploratory BET inhibitor blood signature (**DC only**), and for CTCs for enumeration and PD (**DE and DC**); plasma for exploratory PD (**DC only**)
- PD samples: whole blood for exploratory immuno-oncology biomarkers (at selected clinical sites only; see Section **8.2.12).** (**Only in Part 1, DE only: for all patients requiring enzalutamide Lead-in**)
- PD samples: whole blood for exploratory cfDNA and ctDNA
- AEs (**for all patients requiring Lead-in**)
- Qualitative Exploration of Visual Symptoms (see Section **8.2.16)**
- Concomitant medications

Day 1 (Dosing)

- Part 1: ZEN003694 and enzalutamide at least 1 hour before eating or 2 hours after eating
- Part 2: Abiraterone once daily at least 1 hour before eating or 2 hours after eating

Day 1 (Post-dose)

- PK samples for ZEN003694 and enzalutamide (Part 1) or abiraterone (Part 2)
    - 15 minutes (±5 min), 30 minutes (±5 min), 1 hour (±5 min), 2 hours (±10 min), 4 hours (±15 min), 6 hours (±15 min) and 8 hours (±30 min) post-ZEN003694 and enzalutamide (Part 1) or abiraterone (Part 2) doses
- PD samples: whole blood for BET inhibitor gene expression (all patients) at 2 hours (±15 min), 4 hours (±15 min), and 6 hours (±15 min) and Exploratory BET inhibitor blood signature (**DC only**) 4 hours (±15 min) post- ZEN003694 and enzalutamide (Part 1) or abiraterone (Part 2) doses
- Triplicate 12-lead ECG: 1 hour (± 15 min) post-ZEN003694 and enzalutamide (Part 1) or abiraterone (Part 2) doses

- AEs
- Concomitant medications

Day 2 (Pre-dose)

- PK sample for ZEN003694 and enzalutamide (Part 1) or abiraterone (Part 2): 24 hours (±1 hour) after Cycle 1 Day 1 ZEN003694 and enzalutamide (Part 1) or abiraterone (Part 2) doses
- PD sample: whole blood for BET inhibitor gene expression 24 hours (±1 hour) after Day 1 ZEN003694 and enzalutamide (Part 1) or abiraterone (Part 2) doses

Days 2 – 28 (Dosing as per dosing regimen – QD, BID, on/off schedule)

- Part 1: ZEN003694 and enzalutamide daily at least 1 hour before eating or 2 hours after eating
- Part 2: Abiraterone once daily at least 1 hour before eating or 2 hours after eating

  Note: Instruct patients not to take study drug and enzalutamide (Part 1) or abiraterone (Part 2) before their clinic visits on Days 8, 15 and 22.

Note: All assessments and tests/samples described below are to be performed PRE-DOSE, unless specified otherwise, and are to be performed even if dosing is not required (ie., due to an on/off schedule) on the specified study visit day.

Day 8 (Pre-dose)

- Symptom-directed physical examination and weight
- ECOG performance status
- Vital signs (temperature [F°], blood pressure and heart rate)
- Hematology
- Serum chemistries
- PD sample: whole blood for exploratory immuno-oncology biomarkers (at selected clinical sites only) (**Part 1 DE Only**)
- AEs
- Concomitant medications
- Qualitative Exploration of Visual Symptoms (see Section **8.2.16)**

Day 15 (Pre-dose)

- Symptom-directed physical examination and weight
- ECOG performance status
- Vital signs (temperature [Fº], blood pressure and heart rate)
- Hematology
- Coagulation tests
- Serum chemistries
- Serum troponin level
- Triplicate 12-lead ECG
- PK sample for ZEN003694 and enzalutamide (Part 1) or abiraterone (Part 2)
- AEs
- Qualitative Exploration of Visual Symptoms (see Section **8.2.16)**
- Concomitant medications

Day 15 (Dosing)

- Part 1: ZEN003694 and enzalutamide at least 1 hour before eating or 2 hours after eating
- Part 2: Abiraterone once daily at least 1 hour before eating or 2 hours after eating

Day 15 (Post-dose)

- PK samples for ZEN003694 and enzalutamide (Part 1) or abiraterone (Part 2)
    - 15 minutes (±5 min), 30 min (±5 min), 1 hour (±5 min), 2 hours (±10 min), 4 hours (±15 min), 6 hours (±15 min) and 8 hours (±30 min) post-ZEN003694 and enzalutamide (Part 1) or abiraterone (Part 2) doses
- Triplicate 12-lead ECG: 1 hour (± 15 min) post-ZEN003694 and enzalutamide (Part 1) or abiraterone (Part 2) doses
- Part 1 only: Urine collection for renal clearance may be requested by Zenith for up to 8 hours post-ZEN003694 and enzalutamide doses

Day 22 (Pre-dose or in the morning if dosing is not required on this day due to an alternate dosing schedule)

- Symptom-directed physical examination and weight
- ECOG performance status
- Vital signs (temperature [Fº], blood pressure and heart rate)
- Hematology
- Serum chemistries
- PD sample: whole blood for exploratory immuno-oncology biomarkers (at selected clinical sites only) (**Part 1 DE Only**)
- AEs
- Concomitant medications
- Qualitative Exploration of Visual Symptoms (see Section **8.2.16)**

8.1.4 Cycle 2

Part 1: From Cycle 2, Day 1 onward, if the enzalutamide dose is reduced, PK samples are to be obtained 28 Days (±7 Days) following modification at the following time-points: pre-ZEN003964 and enzalutamide doses, and 15 minutes (±5 min), 30 min (±5 min), 1 hour (±5 min), 2 hours (±10 min), 4 hours (±15 min), 6 hours (±15 min) and 8 hours (±30 min) post-ZEN003694 and enzalutamide doses.

Part 2: From Cycle 2, Day 1 onward, if the ZEN003694 or abiraterone doses are modified, optional PK samples are to be obtained at the discretion of the sponsor following modification at the following time-points: pre-ZEN003964 and abiraterone doses, and 15 minutes (±5 min), 30 min (±5 min), 1 hour (±5 min), 2 hours (±10 min), 4 hours (±15 min), 6 hours (±15 min) and 8 hours (±30 min) post-ZEN003694 and abiraterone doses.

Part 1 and Part 2:

Day 1 (Pre-dose)

- Symptom-directed physical examination and weight
- ECOG performance status
- Vital signs (temperature [Fº], blood pressure and heart rate)
- Hematology
- Coagulation tests

- Serum chemistries: including serum testosterone
- Serum troponin level
- PSA
- Urinalysis
- Triplicate 12-lead ECG
- Part 1 only: Ophthalmology assessments (±7 days) (see Section **8.2.16**)
- PK sample for ZEN003694 and enzalutamide (Part 1) or abiraterone (Part 2)
- PD samples: plasma for exploratory PD (**DC only)**
- PD sample: whole blood for Exploratory BET inhibitor blood signature (**DC only**)
- AEs
- Qualitative Exploration of Visual Symptoms (see Section **8.2.16)**
- Concomitant medications

Days 1 – 28 (Dosing as per dosing regimen – QD, BID, on/off schedule, etc.)

- Part 1: ZEN003694 dosing and enzalutamide daily at least 1 hour before eating or 2 hours after eating
- Part 2: Abiraterone once daily at least 1 hour before eating or 2 hours after eating

  Note: Instruct patients not to take study drug and enzalutamide (Part 1) or abiraterone (Part 2) before their clinic visit on Day 15.

Note: All assessments and tests/samples described below are to be performed PRE-DOSE, unless specified otherwise, and are to be performed even if dosing is not required (i.e., due to an on/off schedule) on the specified study visit day.

Day 8 (The Cycle 2, Day 8 visit will only include blood draws for safety laboratory testing and may be drawn after the patient has taken his dose)

- Hematology
- Serum chemistries

Day 15 (Pre-dose)

- Symptom-directed physical examination and weight

- ECOG performance status
- Vital signs (temperature [Fº], blood pressure and heart rate)
- Hematology
- Serum chemistries
- AEs
- Part 1 Only: Qualitative Exploration of Visual Symptoms (see Section **8.2.16)**
- Concomitant medications

Day 22 (The Cycle 2, Day 22 visit will only include blood draws for safety laboratory testing and may be drawn after the patient has taken his dose)

- Hematology
- Serum chemistries

8.1.5 Cycles 3, 4 and onward

Day 1 (Pre-dose)

- Symptom-directed physical examination and weight
- ECOG performance status
- Vital signs (temperature [Fº], blood pressure and heart rate) Hematology (may be drawn after the patient has taken his dose)
- Coagulation tests (may be drawn after the patient has taken his dose)
- Serum chemistries: including serum testosterone (may be drawn after the patient has taken his dose)
- Serum troponin level (may be drawn after the patient has taken his dose)
- PSA (may be drawn after the patient has taken his dose)
- Urinalysis (may be drawn after the patient has taken his dose)
- AEs
- Part 1 Only: Qualitative Exploration of Visual Symptoms (see Section **8.2.16)**
- Concomitant medications

- Cycle 3 Only: Fresh tumor biopsy samples (optional in DE, mandatory in DC) ± 15 days are to be performed on a ZEN003694 dosing day (see Section **8.2.12**). The on-treatment biopsy should be collected 2-4 hours after ZEN003694 administration, if possible.

- Cycle 3 Only: PD samples: whole blood for exploratory cfDNA and ctDNA

Days 1 – 28 (Dosing as per dosing regimen – QD, BID, on/off schedule)

- Part 1: ZEN003694 and enzalutamide at least 1 hour before eating or 2 hours after eating

- Part 2: Abiraterone once daily at least 1 hour before eating or 2 hours after eating

  Note: Instruct patients not to take study drug and enzalutamide (Part 1) or abiraterone (Part 2) before their clinic visit on Day 1 of each cycle.

Day 15 (For Cycles 3 and onwards, the Day 15 visit will only include blood draws for safety laboratory testing and may be drawn after the patient has taken his dose. Day 15 hematology and/or serum chemistries can be waived at Investigator discretion starting in Cycle 6 onward as long as platelets are stable and there are no other laboratory concerns in the opinion of the Investigator.)

- Hematology

- Serum chemistries

8.1.6 Cycle 3 and every other cycle onward (Cycles 5, 7, etc.)

Day 1 (Pre-dose)

- Triplicate 12-lead ECG

8.1.7 Cycle 3 and every 3 cycles onward (Cycles 6, 9, etc.)

Day 1 (Pre-dose)

- PD samples: whole blood for CTCs for enumeration and PD. Note: Additional whole blood for CTCs for enumeration and PD to be obtained at the time of disease progression as well at the time of PSA or radiographic response.

- PD sample: whole blood for Exploratory BET inhibitor blood signature (**DC only**)

- Tumor assessment (see Section **8.2.15**) Imaging for tumor assessments may be scheduled up to 7 days prior to the scheduled clinic visit day.

- Part 1 Only: Ophthalmology assessments: At Cycle 6 and every 6 cycles onward (±7 days) (see Section **8.2.16**)

8.1.8 Unscheduled Visits and Assessments

Any of the following assessments and tests (as well as others) may be performed as clinically indicated or to assess PD/biomarker responses as agreed upon by the investigator. Additionally, unscheduled assessments or sample collections may occur during a scheduled visit as required.

- Symptom-directed physical examination and weight
- ECOG performance status
- Vital signs (temperature [Fº], blood pressure and heart rate)
- Hematology
- Coagulation tests
- Serum chemistries
- Urinalysis
- Triplicate 12-lead ECGAEs
- Concomitant medications
- Tumor assessment
- Ophthalmology assessments

8.1.9 End of Treatment Visit

The following assessments should be performed within one week (± 3 days) of discontinuation of ZEN003694 treatment: If a subject's dose was held and treatment was not resumed after a two week period, the scheduling of the EOT visit from the date of last study drug is extended to 14 days ±3 days.

- Symptom-directed physical examination and weight
- ECOG performance status
- Vital signs (temperature [Fº], blood pressure and heart rate)
- Hematology
- Serum chemistries: including serum testosterone
- Serum troponin level

- PSA
- Urinalysis
- PD sample: plasma for exploratory PD (**DC only**)
- PD sample: whole blood for Exploratory BET inhibitor blood signature (**DC only**)
- PD samples: whole blood for CTCs for enumeration and PD at time of disease progression and time of PSA or radiographic response
- PD samples: whole blood for exploratory cfDNA and ctDNA
- Part 1 Only: Ophthalmology assessments (±7 days) (see Section **8.2.16**)
- Qualitative Exploration of Visual Symptoms (see Section **8.2.16)**
- AEs
- Concomitant medications
- Fresh tumor biopsy sample (optional during dose escalation and dose confirmation). The biopsies are to be collected at the time of disease progression, if possible**.** The biopsy collected at the time of progression should be collected 2-4 hours after ZEN003694 administration, if possible.
- Tumor assessment (if not performed within the last 3 months)

8.1.10 Safety Follow-up Visit

Thirty days after the End of Treatment visit or prior to beginning a new anti-cancer treatment, whichever occurs first. If a new cancer therapy is started within 7 days following the End of Treatment visit, the Safety Follow-up visit is not required. The patient should return to the clinic for a final safety evaluation, including the following assessments:

- Symptom-directed physical examination and weight
- ECOG performance status
- Vital signs (temperature [F°], blood pressure and heart rate)
- Hematology
- Serum chemistries: including serum testosterone
- Urinalysis

- PSA
- Part 1 Only: Ophthalmology assessments (see Section **8.2.16**) (±7 days Collected at Safety Follow-up only if EOT assessments were abnormal or if there were visual disturbances)
- Part 1 Only: Qualitative Exploration of Visual Symptoms (see Section **8.2.16)**
- AEs
- Concomitant medications

8.2 Study Assessments

8.2.1 Informed Consent

The Investigator or designee must present and explain the study protocol to prospective study patients before the screening procedures are performed. The ICF presented to the patient must be in a language that the patient can read and understand. Once the patient has had an opportunity to read the ICF, the Investigator or designee must be available to answer any questions the patient may have regarding the study protocol and procedures. The Investigator or designee must explain that the patient is not obliged to enter the study, and is free to withdraw from it at any time for any reason. If new safety information becomes available and results in significant changes in risk/benefit assessment, the ICF should be reviewed and updated if necessary. Under this circumstance, all patients, including those already being treated, should be given the new information, given a copy of the revised ICF, and allowed to re-evaluate their consent to continue in the study.

A copy of the signed and dated ICF will be provided to the patient. The Investigator will retain the original signed ICF.

8.2.2 Inclusion/Exclusion Criteria

Review the inclusion/exclusion criteria (see Section **4**) at the Screening visit to ensure that the patient qualifies for the study. The patient may be enrolled into the study if inclusion criteria are met and none of the exclusion criteria are met.

8.2.3 Medical History and Demographics

Obtain a complete medical history (significant past and ongoing conditions) including cancer history, prior PSA data, prior cancer treatments and surgeries, and demographic information at the Screening visit. Previous history of allergies/ allergic reactions should also be captured on the Medical History eCRF.

8.2.4 Physical Examination/Symptom-directed Physical Examination

Physical examination including ears/eyes/nose/throat/neck, respiratory, cardiovascular, gastrointestinal, musculoskeletal, central and peripheral nervous system, and dermatologic assessments will be performed at the Screening visit. A symptom-directed physical examination, including evaluation of new symptoms and follow-up findings from previous physical examinations, should be performed at each study visit pre-ZEN003694 and enzalutamide (Part 1) or abiraterone (Part 2) dosing per the Schedule of Events.

8.2.5 Height and Weight

Height (cm) should be recorded only at the Screening visit and weight (kg) measurements should be measured per the Schedule of Events.

8.2.6 ECOG Performance Status

ECOG performance status will be assessed using the criteria described in **Appendix 1**.

8.2.7 Vital Signs

Vital signs include temperature (Fº), blood pressure and heart rate.

8.2.8 Laboratory Parameters

The following laboratory parameters will be performed at the indicated time points in the Schedule of Events (**Table 1** & **Table 2**). The Investigator must evaluate all results outside the reference range and determine the clinical significance (clinically significant or not clinically significant) of each result.

- Hematology: hemoglobin, hematocrit, red blood cell count, while blood cell count, neutrophils (absolute), lymphocytes (absolute), monocytes (absolute), eosinophils (absolute), basophil (absolute), mean corpuscular volume and platelet count
- Coagulation tests: INR or PT and PTT
- Serum chemistries: albumin, ALT, AST, alkaline phosphatase, amylase, bicarbonate, total bilirubin, blood urea nitrogen, calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), lipase, sodium, potassium, phosphorus and magnesium. Serum testosterone at Screening visit, Day 1 of each Cycle, EOT, and Safety Follow-up.
- Serum troponin: serum samples will be drawn for analyses of troponin T and/or I proteins, based on local laboratory procedure. For any individual patient, the same method will be used at each timepoint.
- PSA

- Urinalysis: dipstick with micro-analysis if clinically indicated

Note: Day 15 safety labs (hematology and/or serum chemistries) can be waived at Investigator discretion starting in Cycle 6 onward as long as platelets are stable and there are no other laboratory concerns in the opinion of the Investigator.

8.2.9 Echocardiogram or MUGA

Echocardiogram or MUGA scan with left ventricular ejection fraction will be obtained during the Screening period.

8.2.10 12-lead ECG

Triplicate 12-lead ECGs will be obtained at the indicated time points in the protocol and Schedule of Events. Note: The timing of post-dose ECG assessments in Cycle 1 on Days 1 and 15 may be adjusted so that they are performed around the C_{max} and C_{ss} of ZEN003694 and the active metabolite, ZEN003791. This adjustment to the timing of the ECG assessments will occur no later than the start of the third dose level. This will enable a more accurate estimation of the time to maximum concentration (T_{max}) of ZEN003694 from the PK data obtained from the patients in Dose Levels 1 and 2.

8.2.11 Pharmacokinetic Sampling

Plasma samples will be collected to assess the PK properties of ZEN003694 and the metabolite ZEN003791,

PK analyses of plasma ZEN003694 and ZEN003791 will be performed at the following timepoints:

- Pre-ZEN003694 and enzalutamide (Part 1) or abiraterone (Part 2) dose, 15 minutes (±5 min), 30 minutes (±5 min), 1 hour (±5 min), 2 hours (±10 min), 4 hours (±15 min), 6 hours (±15 min) and 8 hours (±30 min) post-ZEN003694 and enzalutamide (Part 1) or abiraterone (Part 2 doses

PK analyses of urine ZEN003694 and its metabolites, including ZEN003791 will be performed on C1D15 for up to 8 hours post-dose in the Dose Confirmation phase at the direction of Zenith.

Plasma and urine concentrations will be determined by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) bioanalytical method. Samples will be collected as indicated in the Schedule of Events and the laboratory manual. Exploratory analyses for other metabolites may be conducted by Zenith and reported separately.

Part 1: PK properties of enzalutamide and the metabolite des-methyl enzalutamide will be assessed

PK analyses of plasma enzalutamide and des-methyl enzalutamide will be performed at the following timepoints:

- Pre-enzalutamide and ZEN003694 dose, 1 hour (±5 min), 2 hours (±10 min), 4 hours (±15 min) and 8 hours (±30 min) post- ZEN003694 and enzalutamide doses

If enzalutamide dose is reduced at any time after Cycle 1, PK samples are to be obtained 28 Days (±7 Days) following modification: pre-ZEN003964 and enzalutamide doses, and 15 minutes (±5 min), 30 min (±5 min), 1 hour (±5 min), 2 hours (±10 min), 4 hours (±15 min), 6 hours (±15 min) and 8 hours (±30 min) post-ZEN003694 and enzalutamide doses.

Part 2: PK analyses of abiraterone will be performed at the following timepoints:

- Pre-abiraterone and ZEN003694 dose, 15 minutes (±5 min), 30 minutes (±5 min), 1 hour (±5 min), 2 hours (±10 min), 4 hours (±15 min), 6 hours (±15 min) and 8 hours (±30 min) post-ZEN003694 and abiraterone doses

Unscheduled plasma samples for PK analysis may be requested by Zenith following ZEN003694 or abiraterone dose changes.

8.2.12 Pharmacodynamic Sampling

Blood samples will be drawn for analyses of CTCs (enumeration and PD), cell-free DNA and circulating tumor DNA, exploratory biomarkers and BET inhibitor gene expression profile as indicated in the Schedule of Events. Tumor tissue will be obtained for histological and immunohistochemical analyses, expression of MYC, GR and AR, and RNA sequencing analysis to identify somatic mutations, alternative splicing, fusions and alterations in gene expression. Tumor tissue will be obtained as indicated in the Schedule of Events. Protocols for blood collection and processing whole blood, plasma and CTCs; tumor biopsy; tissue collection; and all sample storage and transportation will be provided in the study reference manual.

- **Whole Blood CTC:** Whole blood will be collected for the following analyses: CTC enumeration, AR-N/AR-C expression to assess AR splice variants.

  CTCs will be identified and quantified ("enumerated") on the basis of nuclear staining with 4,6-diamidino-2-phenylindole, anti-cytokeratin and anti-CD45 antibodies (which distinguishes $CD45^-$ epithelial cells from CD45 leukocytes). Slides will be prepared and analyzed for CTC enumeration and 5-plex AR-N/AR-C expression (dose confirmation phase only).

  One of the resistance mechanisms of ADT is the synthesis of constitutively active AR splice variants lacking the canonical ligand binding domain. Since BETi are predicted to exert anti-tumor activity on both AR (native form) and ligand-independent AR splice variants, it is predicted that ZEN003694 would have anti-tumor activity in patients independent of AR splice isoforms. Monitoring the AR variants will provide important

clinical data regarding the activity of BETi on mCRPC patients with AR variants (**Ware, Garcia-Blanco, Armstrong, & Dehm, 2014**). Furthermore, an increase in the AR splice variants has been associated with resistance to enzalutamide and abiraterone (**Antonarakis et al., 2014**), which is the patient population selected for treatment with ZEN003694.

- **Plasma:** Plasma samples will be collected and banked for biomarker analysis. Plasma samples will be analyzed for protein-based biomarkers using either the Myriad RBM OncoMAP (124 analytes) or the Somalogic Somascan (~1000 analytes). The objective will be to find plasma-based biomarkers with potential correlation to tumor response, which will be further evaluated in Phase 2. In addition, patients that show response (i.e., decrease tumor mass or CTCs) will be analyzed for metabolites and exosomes. Samples will be analyzed in batch upon completion of the dose confirmation phase. Plasma biomarkers correlating with AR versus AR splice variants may also be identified with this analysis.

- **Whole blood BETi gene expression analysis:** Whole blood will be collected. In Cycle 1, RNA will be extracted from these tubes and expression of 6 BETi responsive genes, along with a housekeeping control gene (cyclophilin), will be measured using quantitative polymerase chain reaction (qPCR). Preclinical studies with normal and patient whole blood have shown that the expression of 5 of these genes (MYC, BCL2, chemokine (C-C motif) receptor 1[CCR1], interleukin 1 receptor antagonist [IL1RN], G protein-coupled receptor 183 [GPR183]) is inhibited in a BETi (ZEN003694) dose-dependent manner, while a sixth gene, histone gene cluster 1, H2BE histone family member E (HIST2H2BE), increases in a ZEN003694 dose-dependent manner. Monitoring the expression of these genes at baseline, 2, 4, 6 and 24 hours after ZEN003694 and enzalutamide administration will provide important PD data to help determine when active drug concentrations have been attained.

- **Exploratory whole blood cfDNA and ctDNA:** Whole blood will be collected from patients to isolate plasma and the buffy coat. The plasma will be used to purify cfDNA and compare to DNA extracted from the buffy coat in order to identify circulating DNA that is derived from the tumors (ctDNA). It will possibly allow a survey of the different mutations present in tumors across the body, monitor changes in the tumor cell population over the course of the trial, and possibly identify mechanisms of resistance to ZEN003694. Changes in the percentage of ctDNA fraction and mutational spectrum of ctDNA over the course of the treatment will be monitored and compared to the biopsies obtained from the same patient to potentially establish correlations with the patient's response, similarly to what has been recently published for ARSIs (**Annala et al., 2018; Wyatt et al., 2017; Wyatt et al., 2016)** and PARP inhibitors (**Goodall et al., 2017; Quigley et al., 2017)**).

- **Exploratory BETi blood signature:** Whole blood will be collected at different time-points during the trial per the **Table 1 & Table 2**: Schedule of Events to measure changes in gene expression during the course of the study. To measure gene expression, RNA will be extracted from the blood, and all the RNA molecules will be sequenced by RNA-Seq to allow quantification of all the genes expressed in the sample. By comparing the changes in RNA expression through the study, potential genes associated with response and/or resistance to ZEN003694 might be identified, and they are sometimes referred to as biomarkers. These biomarkers could be further evaluated in future studies and used to predict responses to ZEN003694, and/or select a treatment regimen using whole blood.

- **Tumor Biopsy:** Metastatic tumor biopsies will be taken with core needle or excisional biopsy. Fine needle aspiration is not allowed. It is encouraged that 4 core samples be collected from a single site with a minimum of 2 core samples collected. The biopsy sample will be split into two components, one formalin fixed for histological and immunohistochemical analyses, as well as possible DNA mutation analysis. The other component will be flash frozen for RNA isolation and sequencing. In addition to the typical hematoxylin and eosin staining for tumor morphology and histologic classification, the expression and nuclear localization of AR, GR and MYC will be assessed by immunohistochemistry. For RNA sequencing analysis, paired end sequencing (100 bp, 45-50x10^6 reads) will be used to identify somatic mutations, alternative splicing, fusions and alterations in gene expression. An RNA aliquot will be taken from the frozen samples to detect the presence of the AR-V7 splice variant as well. In the dose confirmation phase, sampling accessible tumors is mandatory at baseline and during the course of treatment and optional at disease progression to help identify potential biomarkers for tumor response as well as tumor resistance. Archival tumor samples (initial diagnostic biopsy or biopsy at time of prostatectomy or other resected tissue), if available, will be collected during the Screening period through the end of Cycle 2 or the End of Treatment, whichever occurs first.

- **Immuno-Oncology samples**: At selected sites only in dose escalation of Part 1, whole blood will be collected for the following analyses: T-cell receptor (TCR) sequencing in PBMCs and flow cytometry in PBMCs. TCR sequencing will analyze both clonotype frequency and diversity of tumor-specific T-cell responses in the entire TCR repertoire. Flow cytometry will measure populations of T-helper subsets, cytotoxic and memory T-cells, T-regs, B-cells, myeloid cell populations as well as LAG3, CTLA4 and PD-1 cell populations. In addition, PD-L1 and CD8 cells will be possibly evaluated by immunohistochemistry in tumor samples.

8.2.13 Adverse Events

Adverse events will be collected as defined in Sections **10.1**, **10.2** and **10.3**.

8.2.14 Concomitant Medications

All prior cancer-related treatment and procedures will be captured on the eCRFs. All concomitant medications (dose and regimen) taken during the course of the study must be recorded on the Concomitant Medications eCRF. In addition, any medications taken 21 days prior to enrollment in the study should be recorded on the Concomitant Medications eCRF.

8.2.15 Tumor Assessment – Imaging/Radiologic Evaluation

Whole body radionuclide imaging (Tech-99) and cross-sectional imaging of the chest/abdomen/pelvis should be performed in accordance with institutional standards. Use of intravenous contrast is required unless contraindicated. Magnetic resonance imaging (MRI) may be substituted for computed tomography (CT) per the Investigator's discretion. Disease status should be assessed using the PCWG2 criteria (see **Appendix 3**).

Note: To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments no less than 4 weeks after the criteria for response are first met.

8.2.16 Ophthalmology Assessments

Ophthalmology assessments are to be performed by an ophthalmologist and will include:

- Part 1: Ophthalmic history, Snellen best corrected visual acuity (including refraction, if needed), color vision testing (using standard HRR pseudoisochromatic plates), pupillometry, confrontational visual field testing, intraocular pressure (using Goldmann tonometry or TonoPen tonometry), external eye and ocular motility exam and slit lamp biomicroscopy, indirect ophthalmoscopy, OCT optic nerve and macula tests, fundus photography, and other exams as clinically indicated.
- Part 2: Ophthalmic history, Snellen best corrected visual acuity (including refraction, if needed), color vision testing (using standard HRR pseudoisochromatic plates), pupillometry, OCT optic nerve and macula tests, fundus photography, and other exams as clinically indicated.

In both parts of the study, completion of the Qualitative Exploration of Visual Symptoms form (provided by the Sponsor) is required at time-points detailed in the Schedule of Assessments.

At any time during the study should a clinically meaningful change in visual symptoms occur, unscheduled ophthalmology assessments are to be performed.

9. WITHDRAWAL OR EARLY TERMINATION OF PATIENTS

Patients are free to withdraw from study participation at any time for any reason. Patients may discontinue treatment with ZEN003694 either at their request, at the discretion of the Investigator for medically indicated reasons or for protocol noncompliance.

In the event of early termination, the patient should be instructed to report to the clinic as early as possible but within 1 week after the decision to terminate from the study has been made or for the next scheduled clinic visit. All End of Treatment visit procedures (see Section **8.1.9**) and all Safety Follow-up visit procedures (see Section **8.1.10**) are to be conducted. The Investigator shall make his or her best efforts to perform these procedures. The Investigator should make all attempts to accurately identify the reason a patient withdrew from the study, while respecting the patient's privacy. The primary reason for the patient discontinuation should be documented as one of the following:

- Clinical progression by PCWG2 criteria
- Clinical progression by PCWG2 criteria with PSA progression
- Radiographic progression by PCWG2 criteria
- Radiographic progression by PCWG2 criteria with PSA progression
- DLT
- Adverse event
- Treatment with or need for prohibited concomitant medication
- Withdrawal by patient
- Withdrawal by physician
- Non-compliance
- Lost to follow-up
- Death

10. SAFETY ASSESSMENTS

Safety parameters monitored and recorded during this study include, physical examination findings, weight, vital signs, ECOG performance status, ECGs, AEs, laboratory variables (hematology, serum chemistries, serum troponin, coagulation tests and urinalysis).

10.1 Adverse Event and Suspected Unexpected Serious Adverse Reaction Definitions

10.1.1 Adverse Event

An AE is any unfavorable or unintended sign, symptom, or disease temporally associated with the use of a pharmaceutical product (i.e., study drug), whether or not considered related to the pharmaceutical product.

The recording of AEs will begin at the start of the administration of the first dose of enzalutamide in the Lead-in phase of the study. AEs should record the development of an undesirable medical condition, worsening of a pre-existing medical condition and any change in severity (increase or decrease) of a previously recorded AE, during or following exposure to study drug, regardless of relationship to study drug. See Section **10.3** for additional information.

10.1.2 Serious Adverse Event

A serious adverse event (SAE) is any AE that:

- Results in death
- Is life-threatening
    - A life-threatening SAE is any AE that places the patient at immediate risk of death from the reaction as it occurred, as assessed by the Investigator. This definition does not include a reaction that might have caused death if it occurred in a more severe form.
- Requires in-patient hospitalization or prolongs existing hospitalization
    - For the purposes of this protocol, any hospital admission will be considered an in-patient hospitalization, regardless of duration. An emergency room visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalizations for a procedure scheduled before study enrollment (first dose of study drug) or elective procedures scheduled during the study. However, unexpected complications that occur during elective surgery should be recorded as AEs and assessed for seriousness.
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- Results in a congenital anomaly or birth defect
- Is any other important medical event
- Other medical events may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes in the SAE definition. Examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization of the patient, or the development of drug dependency or drug abuse.

10.1.3 Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is any AE for which there is evidence to suggest a causal relationship between the study drug and the AE (e.g., assessed as possibly or probably related), and which is both unexpected and serious. An unexpected adverse reaction (i.e., any untoward and unintended response to the study drug) is one for which the nature and severity is inconsistent with the applicable reference safety information (e.g., Investigator's Brochure).

10.2 Reporting Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions

Report all SAEs and SUSARs to Drug Safety **WITHIN ONE BUSINESS DAY** of discovery or notification. Record event information on the SAE Report Form, and submit the completed form with any other available pertinent information (e.g., hospital records, laboratory results, etc.) to Drug Safety (contact information are provided in the study reference manual). The minimum required information for an initial report is:

- Reporter's name and contact information
- Protocol number
- Site and patient identification information
- Event term(s) (with a brief summary of the event[s] and causality assessment)

If additional follow-up information is required or becomes available for a previously reported SAE or SUSAR, a follow-up SAE Report Form with the new information should be prepared and submitted **WITHIN ONE BUSINESS DAY**.

For hospitalizations, all attempts to obtain the hospital record should be documented in the study file. Complete an SAE Report Form with any known information on the hospitalization, however minimal, and submit it to Drug Safety (detailed contact information is provided in the study reference manual).

10.2.1 Disease-related Events That Are Endpoints

For the purposes of this study, progression of the patient's underlying disease ("disease progression") should generally not be reported as an AE or SAE. However, if the Investigator determines that there is evidence suggesting a causal relationship between the event and the study medication, immediately report the event to Drug Safety and record as an AE or SAE.

Any event that results in death is to be reported as an SAE. Death is an outcome of an adverse event and not an adverse event in itself. The underlying event leading to death is reported as the SAE.

10.3 Adverse Events

Events that occur before the first administration of study drug are not considered AEs, by definition (Section **10.1.1**); record these events on the Medical History CRF.

The Investigator or a qualified designee will question and examine patients for evidence of AEs. Patients should not be asked about specific AEs. Instead, they should be asked general questions (e.g. "How have you been feeling since your last visit?"). Record all AEs on the AE CRF. If a previously reported AE changes in severity, record the change in the AE severity on the AE CRF.

For an event to be recorded as an AE, the onset must occur during or after the patient's first exposure to study drug and no later than 30 days after the last study drug dose. However, there is no limit on reporting SAEs considered reasonably related to ZEN003694. Immediately report all SAEs and deaths to Drug Safety (Section **10.2**). This requirement includes deaths within 30 days of the last dose of study drug, or before the last formal follow-up contact, whichever occurs later. The Investigator should follow all AEs that are considered reasonably related to study drug until resolution or stabilization. All other AEs should be followed until resolution or stabilization or until the final visit, whichever occurs first.

Record syndromes rather than individual signs or symptoms in order to avoid double reporting of events and facilitate meaningful interpretation of data. For example, a patient presenting with rhinitis, fever, and headache should be reported as having "flu-like symptoms," without independently recording each accompanying sign. When no clearly recognizable clinical syndrome can be described, record individual clinical signs and symptoms.

All AEs that occur during the study should be treated appropriately to protect and ensure the patient's well-being. If such treatment constitutes a deviation from this protocol, Drug Safety must be notified and the Investigator should comply with applicable Ethics Committee (EC) or Institutional Review Board (IRB) reporting requirements.

The Investigator is responsible for determining whether or not an AE is severe enough to require the patient's removal from treatment. A patient may also voluntarily withdraw from treatment because of an AE. If either occurs, the patient must receive appropriate medical care, and the

Investigator must strongly encourage the patient to return to the study site for the final protocol-specified visits and assessments, and to continue returning to the study site for follow-up evaluations until the AE resolves or stabilizes. All AEs, serious or not, that result in permanent withdrawal from the study treatment should be immediately reported to Drug Safety.

Zenith will conduct reviews of all available AEs approximately once every 3 months. During dose escalation, these review timelines may be modified to coincide with enrollment and dose-escalation safety data. The study sites are to ensure timely entry of AEs on the CRFs to facilitate these reviews.

10.3.1 Classification of Adverse Events by Severity

The Investigator must categorize the severity of each AE using the NCI CTCAE Version 4.03 (see **Appendix 2**).

It is important to distinguish between AE seriousness and severity; these terms are not interchangeable. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section **10.1.2**.

10.3.2 Classification of Adverse Events by Relationship to Study Drug

For each AE, the Investigator must decide whether there is a reasonable possibility that the event was caused by administration of ZEN003694 (i.e., that the event was a suspected adverse reaction). The Investigator should make this decision after careful consideration of the following questions:

- Does the AE follow a reasonable temporal sequence from administration of study drug?
- Can the AE be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other therapy?
- Do the AE symptoms disappear or decrease on cessation of study drug or reduction in study drug dose? (There are exceptions when an AE does not disappear on discontinuation of the drug, yet drug relatedness clearly exists [e.g., bone marrow depression, fixed drug eruptions, tardive dyskinesia, etc.]).
- Does the AE reappear or worsen when the study drug is re-administered?
- Does the AE follow an expected response pattern based on the established pharmacologic and toxicologic effects of the study drug?
- Does the AE follow an expected response pattern based on the known effects of other products in the same class?

For this assessment, the Investigator will classify each AE as one of the following:

- **Yes, Related:** The AE is definitely related or even considered possibly or probably related to study drug administration.
- **Not Related:** The AE is clearly due to other causes (e.g. concurrent medication, underlying disease, etc.).

10.4 Abnormal Laboratory Results

Abnormal laboratory results may occur in the context of an AE that is a clinical syndrome (e.g., elevated BUN and creatinine in the setting of an AE of renal failure, or elevated AST/ALT in the setting of an AE of hepatitis). In these cases, do not record the abnormality itself as an AE.

However, in the absence of an AE that encompasses an observed abnormal laboratory result, report the abnormality as an AE if the Investigator judges it to be clinically significant for the patient.

For the purposes of this study, the criteria for a "clinically significant" abnormal laboratory result are any of the following:

- It leads to DLT
- It results in any therapeutic intervention
- It is judged by the Investigator to be of other particular clinical relevance

10.5 Overdose

All study drug will be administered orally.

There is no data regarding ZEN003694 overdose in humans. An overdose and AEs should be treated as per standard medical practice.

Dosing details should be captured on the Study Drug CRF. If the patient receives a dose of a study drug that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented on the AE CRF and on a SAE form as appropriate. Do not capture the event on the AE CRF or SAE form if the patient is not symptomatic.

Should an overdose occur, the Investigator should also monitor the patient with appropriate blood counts and serum chemistry tests and should also provide supportive therapies as necessary.

10.6 Study Safety Monitoring and Dose Escalation or Modification

The CRC will review safety and available PK data (e.g., C_{max} and AUC) for each cohort in the dose escalation phase to decide when it is permissible to open a new cohort per the study design

described in the protocol. Safety data will include but are not limited to SAEs, AEs and laboratory (protocol specified or ad hoc) data, as well as additional information provided by the treating Investigators. Additionally, the accruing safety data for all patients to date will be included in the decision making process for dose escalation or modification. Dose escalation or modifications will be allowed in the absence of an unreasonable and significant risk of illness or injury to patients. In addition, Zenith will review the study safety data on an ongoing basis. An independent specialist may participate in the safety review, if appropriate.

10.7 Reporting Safety Information to the Institutional Review Board

Zenith or its designee will provide written safety reports or other safety-related communications to the Investigator. The Investigator will ensure that these reports are reviewed and processed in accordance with regulatory and EC/IRB requirements and archived in the site's study file.

At the completion or early termination of the study, the Investigator will submit a final report to the EC/IRB in accordance with local requirements.

11. STUDY ENDPOINTS

11.1 Primary Endpoints

- Safety profile of ZEN003694 in combination with enzalutamide (Part 1) and abiraterone (Part 2)
- DLT characteristics and MTD determination for ZEN003694 in combination with enzalutamide (Part 1) and abiraterone (Part 2, if MTD is determined)
- RP2D of ZEN003694 in combination with enzalutamide (Part 1) and abiraterone (Part 2) for further clinical investigation

11.2 Secondary Endpoints

- Part 1: Plasma concentrations of ZEN003694, the active metabolite ZEN003791 and enzalutamide and the active metabolite des-methyl enzalutamide. The following PK parameters, at a minimum, will be calculated as appropriate: $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$, C_{max} and minimum or trough concentration (C_{min}), dosing interval, and T_{max} and half-life ($t_{1/2}$)
- Part 2: Plasma concentrations of ZEN003694, the active metabolite ZEN003791 and abiraterone. The following PK parameters, at a minimum, will be calculated as appropriate: $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$, C_{max} and minimum or trough concentration (C_{min}), dosing interval, and T_{max} and half-life ($t_{1/2}$)
- Overall response rate, complete response (CR) and partial response (PR) by PCWG2 criteria
- PSA response by PCWG2 criteria
- Median progression-free survival by PCWG2 criteria
- CTC response (dose confirmation)

11.3 Exploratory Endpoints

- Baseline and change from baseline post-treatment in BET gene expression in whole blood
- Baseline and change from baseline post-treatment in quantification of AR splice variants in blood (dose confirmation) and post-treatment in tumor tissue* and response (CR, PR, PD)
- Baseline and change from baseline post-treatment in MYC expression in tumor tissue* and response (CR, PR, PD)

- Baseline and change from baseline post-treatment in GR expression in tumor tissue* and response (CR, PR, PD)
- Possible relationship of baseline tumor abnormalities (such as mutations, translocations, mRNA, protein expression and localization), in circulating tumor DNA (ctDNA), circulating tumor cells (CTC) and tumor biopsies and/or on-treatment changes with any observed antitumor activity
- Baseline and change from baseline post-treatment in immuno-oncology biomarkers, if observed.
- Part 1: Correlation between ZEN003694, ZEN003791, enzalutamide and des-methyl enzalutamide plasma exposure levels and PD responses
- Part 2: Correlation between ZEN003694, ZEN003791, abiraterone plasma exposure levels and PD responses
- Correlation between PSA and radiographic response (CR, PR, PD)

***** Tumor biopsies are optional at baseline, on-study treatment, and at the time of progression in dose escalation; mandatory at baseline, on-study treatment, and optional at the time of progression in dose confirmation

12. STATISTICS

12.1 General Considerations

The primary statistical analysis of the data will be descriptive in nature. For continuous variables this means calculation of the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by patient counts and related percentages. For ordinal-scaled variables, a combination of the above may be employed as appropriate: frequency and percentage of observations within a category and means and standard deviations of the scores of the categories. For categorical and ordinal variables, percentages will be calculated based on non-missing data.

Based on the characteristics of the study design and lack of a concurrent control arm, formal testing of treatment effects (i.e., inferential statistics) will not be performed. However, some measures will be summarized by both point estimates and the associated 95% confidence intervals.

12.2 Sample Size Determination

A conventional algorithm (3+3 patients per dose level) will be used to identify the MTD, escalating on 0 of 3 or 1 of 6 DLTs, and de-escalating if 2 DLTs are encountered. The MTD will be the highest dose level at which 0 of 3 or 1 of 6 patients experience a DLT, with the next higher dose having at least 2 of 3 or 2 of 6 patients experiencing a DLT. With this design, there is a 71% chance of escalation if the true but unknown rate of DLT is 20%, and less than 50% chance of escalation if the true but unknown rate of DLT is higher than 30%.

Part 1: Approximately 40 patients may be enrolled in the dose escalation phase of the study. Up to 40 patients in the dose confirmation phase may be enrolled at the MTD or RP2D. The sample size is sufficient to support preliminary safety and pharmacologic assessments.

Part 2: Approximately 15 patients may be enrolled in the dose escalation phase of the study. Up to 40 patients in the dose confirmation phase may be enrolled at the MTD or RP2D. The sample size is sufficient to support preliminary safety and pharmacologic assessments.

12.3 Analysis Populations

Safety population: Patients who receive at least one dose of ZEN003694.

DLT population: Patients who experience a DLT as defined in Section **5.1.2**. Patients who experience a DLT within the first cycle of treatment and drop out of the study will be considered evaluable for DLT and will not be replaced.

Part 1: No dose modification of enzalutamide (160 mg) is permitted during Cycle 1, including the 14-day Lead-in period; patients requiring dose modification during Cycle 1 must discontinue the study and will be replaced. Patients, who for reasons other than a DLT, discontinue the study prior to completion of the first cycle will be considered unevaluable and will be replaced.

Part 2: No dose modification of abiraterone (1000 mg) is permitted during Cycle 1, including the 14-day Lead-in period; patients requiring dose modification during Cycle 1 must discontinue the study and will be replaced. Patients, who for reasons other than a DLT, discontinue the study prior to completion of the first cycle will be considered unevaluable and will be replaced.

12.4 Data Handling

Clinical data will be entered into a clinical data management system (CDMS), involving electronic data capture. Criteria for such a CDMS are that it is Part 11 compliant, web-based and supports remote monitoring. The handling of data, including data quality assurance, will comply with regulatory guidelines, and will be defined in the study-specific data management plan (DMP). The DMP will define roles and responsibilities in regard to data quality processes and expectations, from study start-up to final database lock.

12.5 Statistical Analyses

Prior to the analysis of the final study data, a detailed statistical analysis plan (SAP) will be written. Detailed information regarding analysis datasets, summarization of the data and analyses will be provided in the SAP. The SAP will contain any modifications to the analyses described in this section.

13. QUALITY CONTROL AND QUALITY ASSURANCE

Prior to participation in this study, investigational sites and Investigators will be evaluated for appropriate qualifications and ability to properly execute the study. Each investigational site must undergo proper training on the study protocol and ancillary study procedures/documents through participation in an initiation visit or Investigator meeting. Such training must take place before any patients are enrolled at that site. Initiation visits and Investigator meetings will include but may not be limited to review of Good Clinical Practice (GCP) guidelines, study drug procedures, data collection requirements and patient eligibility requirements.

Zenith or designee will make periodic visits to the investigational site to assess compliance with study procedures and regulatory requirements; to ensure that the safety, welfare and privacy of patients are being protected; and to verify the accuracy and integrity of the study data.

In addition, Zenith will periodically review the study data to ensure that data are being appropriately collected and reported. Logic checks will be also programmed and run to identify errors and data discrepancies. Discrepancies will be reviewed with investigational site personnel, corrections will be made to the database, and a validated audit trail will be maintained. The database will be locked and audited before it is released for analysis.

13.1 Study Monitoring

Before the initiation of the study, a representative from Zenith will visit the investigational site to:

- Determine the adequacy of the facilities
- Discuss the responsibilities of the Investigator(s) and other personnel involved with the study with regard to protocol adherence and the responsibilities of Zenith and their representatives

During the study, the Study Monitor will have regular contact with the investigational site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded on the CRFs, and that the investigational product accountability is being performed.
- Perform source data verification (a comparison of the data on the CRFs with the patient's records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each patient e.g., clinic charts. Incorrect or missing entries on to the CRFs will be queried and must be corrected immediately.

13.2 Audit and Inspection

During or after the study is completed, Zenith, its representatives or a Regulatory Authority may wish to carry out an audit or inspection. These representatives must have the same access to study data and patient source data as the Study Monitor.

13.3 Regulatory Authority Correspondence

The Investigator will notify Zenith or designee immediately following any regulatory contact with the investigational site. The Investigator will provide requested copies of all correspondence with the Regulatory Authority that may affect the review of the current study (e.g., Form 483, Inspectional Observations). Zenith or their designee reserves the right to be at the investigational site during any regulatory inspection that involves this protocol.

14. ETHICAL AND LEGAL ISSUES

14.1 Statement of Compliance

This study will be conducted in accordance with the following:

- Protocol-related and study-related documents
- GCP as outlined in the International Conference on Harmonization (ICH) E6 guideline and regional regulations
- Regional required patient data protection laws and regulations
- Applicable regional regulations

14.2 Ethics Committee or Institutional Review Board Approval

The Principal Investigator at each site is responsible for obtaining regional EC or IRB approval for the final protocol, Zenith-approved ICF/assent, patient information sheet, if applicable, and any advertisements to recruit patients. Written approval of these documents must be obtained from the EC/IRB and a copy submitted to Zenith before any patient is enrolled at an investigational site.

The Principal Investigator is also responsible for the following interactions with the regional EC/IRB.

- Obtaining EC/IRB approval for any protocol amendments and ICF/assent revisions before implementing the changes
- Providing the EC/IRB with any required information before or during the study
- Submitting progress reports to the EC/IRB as required during the conduct of the study, requesting re-review and approval of the study as needed, and providing copies of all EC/IRB renewal of approvals and relevant communication to Zenith and/or its representative
- Notifying the EC/IRB of all serious and unexpected AEs related to the study medication reported by Zenith and/or its representative, as required
- Notifying the EC/IRB at the end of the study, in accordance with regional guidelines and regulations

14.3 Patient Informed Consent/Assent

The Investigator's draft ICF/assent must be reviewed by Zenith and/or its representative prior to submission to a regional EC/IRB for approval. A copy of the ICF/assent approved by the EC/IRB must be forwarded to Zenith and/or its representative.

The consent of the patient to participate in the study has to be given in writing prior to enrollment. It must be signed and personally dated by the patient, parent, legal guardian or caretaker and by the Investigator, Sub-investigator or study coordinator designated by the Investigator to conduct the informed consent discussion. The signed and dated declaration of informed consent will remain at the Investigators' site and must be safely archived by the Investigator so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated ICF should be provided to the patient prior to participation and the original maintained in the patient's source documents or in a separate archive file for the informed consent documents for the study.

14.4 Patient Compensation for Adverse Effects on Health

Zenith and/or its representative will adhere to regional regulations regarding clinical trial compensation to patients whose health is adversely affected by participation in the study.

14.5 Changes to the Conduct of the Study, Protocol and Study Termination

14.5.1 Protocol Amendments

Changes in the study protocol shall be in the form of written study protocol amendments. These will require the approval of all signatories of the final protocol. Any substantial amendments to the protocol that affect the patient, e.g., changes in procedures/assessments or matters relating to patient safety, require a favorable opinion from the EC/IRB for the study sites prior to implementation. Changes of a purely administrative nature should be notified to the committee(s) as applicable, but do not require formal approval. However, a change to the protocol to eliminate an apparent immediate hazard to the patient may be implemented immediately provided the EC/IRB and applicable Regulatory Authorities are subsequently notified by protocol amendment. Any amendment affecting the patient requires further informed consent from each patient before implementation.

14.5.2 Study Termination

Zenith reserves the right to terminate the study at any time for any reason. The Investigator should notify the EC/IRB in writing of the completion or early termination of the study. Zenith will promptly notify US FDA and other Regulatory Authorities if enrollment is terminated or suspended for any reason. Upon study completion or termination, applicable regulatory reporting requirements will be followed.

15. INVESTIGATOR RESPONSIBILITIES

The Investigators shall be responsible for ensuring that the study is performed in accordance with the protocol, Food and Drug Administration (FDA)/ICH GCP regulations and applicable regional regulatory requirements.

15.1 Staff Training

The Investigator will maintain a record of all individuals involved in the study. He or she will ensure that appropriate training relevant to the study is given to all staff members involved in this study, and that they will receive any new information of relevance to the performance of this study. The Investigator should maintain a list of appropriately trained persons to whom the Investigator has delegated trial-related duties.

15.2 Study Conduct

In signing this protocol, the Investigator agrees to:

- Conduct the study in accordance with the relevant, current protocol and make changes only after notifying Zenith or its representative, except where necessary to eliminate apparent immediate hazards to human patients
- Comply with the ICH guidelines on GCPs plus appropriate regional regulatory laws and requirements
- Personally conduct or supervise the described investigation
- Inform any patients or persons used as controls that the study drugs are being used for investigational purposes
- Ensure requirements relating to obtaining informed consent and EC or IRB approval have been met
- Report to Zenith or its representative any AEs that occur in the course of the investigations, as specified in Section **10**
- Read and understand the Investigator's Brochure, including potential risks and side effects of the drug
- Ensure all associates, colleagues, and employees assisting in the conduct of the study are informed of their obligations in meeting their commitments
- Maintain adequate and accurate records and make these available for inspection by Zenith and/or its representative, or any regulatory agency authorized by law

- Promptly report to the EC or IRB all changes in research activity and all unanticipated problems involving risks to human patients or others
- Comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements
- Administer study drug only to patients who meet study entry criteria and are enrolled in the study, and only according to the guidelines set forth in this protocol

15.3 Recordkeeping

The Investigator is responsible for maintaining adequate records to fully document the conduct of the study, including but not limited to the following:

- All versions of the Investigator's Brochure and the signed protocol and amendments in effect during the conduct of the study
- Signed ICFs/assents
- Source documents including adequate case histories
- Signed, dated and completed CRFs or data collection forms and documentation of data corrections
- Notification of SAEs and related reports
- Investigational product accountability logs and documentation of return of unused and used investigational product, if applicable
- Dated and documented EC/IRB approvals
- Normal laboratory test values and laboratory certifications, if applicable
- Curricula vitae of all clinical Investigators
- Completed Forms US FDA 1572
- Trial initiation documentation
- Delegation of Authority Log
- Signed Signature of Agreement for Protocol and Amendment and agreements between involved parties
- Relevant communication, including that related to the Study Monitor's site visits (e.g., letters, meeting notes, notes from telephone calls)

- Interim, annual or final reports to ECs/IRBs
- Patient screening log, patient identification code list and patient enrollment log
- Audit certificate if applicable

16. PUBLICATIONS

The data and information generated in this study are the exclusive property of Zenith and are confidential.

To avoid disclosures that could jeopardize proprietary rights, the investigator agrees to give Zenith the right to review all manuscripts, abstracts, and presentations related to this study at least 30 days *prior* to their submission for publication or presentation. Authorship among Investigators generally will be based on the extent of significant contribution, including scientific and clinical, to the publication.

17. CONFIDENTIALITY

The Investigators as well as their staff, and all its representatives must agree to maintain the confidentiality of the study at all times and must not reveal information relating to the Investigator's Brochure, protocol, CRFs or associated documents to unauthorized third parties.

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Appendix 1: ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, 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.

Source: (Oken et al., 1982)

Appendix 2: NCI CTCAE Version 4.03 Adverse Event Severity Grading

Grade refers to the severity of the AE. The NCI CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline as shown in the table below.

Adverse Event Severity Grading — NCI CTCAE

	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]
3	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care AD.[b]
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

A semicolon (;) indicates "or" within the description of the grade. A single dash (–) indicates a grade is not available. Not all grades are appropriate for all AEs; therefore, some AEs are listed with fewer than 5 options for grade selection.

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

Appendix 3: Prostate Cancer Clinical Trials Working Group 2 Criteria

MEASUREMENT OF RESPONSE

Measurement of response in patients with measurable disease

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) criteria (**Eisenhauer et al., 2009**). Changes in the sum of the diameters of target lesions of the tumor lesions are used in the RECIST criteria.

> **Note:** lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy. All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 30 days before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Measurable disease/ Target lesions

> All measurable lesions (lesions that can be accurately measured in at least one dimension [longest diameter to be recorded except for target lymph nodes with are measured on the short axis] as ≥ 10mm with spiral CT) up to a maximum of 2 lesions per organ and 5 lesions total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and the suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the LD for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as a reference by which to characterize the objective tumor response.

Lymph node metastases must measure 1.5 cm or greater in short axis diameter to be considered target lesions, while other target lesions must measure 1 cm or greater (with spiral CT scans).

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started (including baseline LD), or the appearance of one or more new lesions

Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s), and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions, and/or unequivocal progression of existing non-target lesions

Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the study chair.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started, including baseline; see table below). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies no less than 4 weeks after the criteria for response are first met. In the

case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum of 12 weeks after study entry.

Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Target Lesions	Non-Target Lesions	New Lesions	Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Evaluation of non-measurable bone disease

Bone scans obtained after the baseline evaluation will be used to evaluate post-treatment changes. Bone scans obtained will be evaluated as either "no new lesions" or "new lesions" on the tumor measurement forms.

a. For the first scheduled reassessment: New lesions at the first scheduled evaluation will require a confirmatory bone scan 6 or more weeks later. If no new lesions are observed on the confirmatory bone scan, study therapy is continued. If additional new lesions are observed, then the patient has experienced progression. Progression in this situation is dated as the time of the first reassessment scan.

b. For subsequent scheduled reassessments: If no new lesions are observed, study therapy will continue. If new lesions are observed, this is evidence of disease progression. Date of progression is the date at which the scan was obtained.

Post-treatment PSA Changes

All patients, with or without measurable or non-measurable disease, will be evaluated for PSA decline. Patients with disease that is not measurable will be eligible for this study and will be assessed for response based on changes in PSA and serial bone scans (if appropriate). The

baseline serum PSA must be at least 2 ng/mL. Patients who show PSA increases will not be evaluated for PSA progression prior to 12 weeks of study therapy.

a. 30% and 50% PSA Decline: PSA decline of at least 30% and 50%, respectively, from baseline confirmed by a second measurement at least 3 weeks later. The reference for these declines should be a PSA measured within 2 weeks prior to starting therapy.

b. PSA Progression: PCWG2 Criteria will be reported. PSA progression occurs when the PSA has increased 25% or greater above nadir and an absolute increase of 2 ng/mL or more from the nadir is documented. Where no decline is observed, PSA progression similarly occurs when a 25% increase from baseline value along with an increase in absolute value of 2 ng/mL or more. Patients will receive a minimum of 12 weeks of therapy prior to being evaluable for this endpoint. PSA progression (without evidence of progression on scans) will not be criteria for discontinuation of study therapy.

c. PSA Response Duration: The PSA response duration commences on the date of the first 50% decline in PSA. The response duration ends when the PSA value increases by 25% above the nadir, provided that the increase in the absolute-value PSA level is at least 5 ng/mL or back to baseline, whichever is lower.

d. Progressive Disease by PSA (as defined by PSA Progression above)

e. Time to PSA Progression: The start of the time to PSA progression is the day treatment is initiated. The end date is the date of the first PSA rise over the determined PSA PD value.

Progressive disease (PD)

Progressive disease will be defined by <u>any one</u> of the following:

a. Appearance of new metastatic lesions outside the bone

b. New metastatic lesions on bone scan confirmed as described above

c. Development of an indication for radiotherapy while on treatment

d. Unequivocal progression of non-target lesions

e. Global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression

Note that PSA progression (as defined above) alone does not meet the criteria for progressive disease.

Source: (Scher et al., 2008)

Appendix 4: XTANDI® Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XTANDI® safely and effectively. See full prescribing information for XTANDI.

XTANDI® (enzalutamide) capsules for oral use
Initial U.S. Approval: 2012

----------RECENT MAJOR CHANGES----------

Warnings and Precautions (5.2)	08/2015
Dose Modifications (2.2)	10/2015

----------INDICATIONS AND USAGE----------
XTANDI is an androgen receptor inhibitor indicated for the treatment of patients with metastatic castration-resistant prostate cancer. (1)

----------DOSAGE AND ADMINISTRATION----------
XTANDI 160 mg (four 40 mg capsules) administered orally once daily. Swallow capsules whole. XTANDI can be taken with or without food. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Capsule 40 mg (3)

----------CONTRAINDICATIONS----------
Pregnancy (4, 8.1)

----------WARNINGS AND PRECAUTIONS----------
- Seizure occurred in 0.9% of patients receiving XTANDI who previously received docetaxel and in 0.1% of patients who were chemotherapy-naive. There is no clinical trial experience with XTANDI in patients who have had a seizure. Permanently discontinue XTANDI in patients who develop a seizure during treatment. (5.1)
- Posterior reversible encephalopathy syndrome (PRES): Discontinue XTANDI. (5.2)

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥ 10%) are asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Astellas Pharma US, Inc. at 1-800-727-7003 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Avoid strong CYP2C8 inhibitors, as they can increase the plasma exposure to XTANDI. If co-administration is necessary, reduce the dose of XTANDI. (2.2, 7.1)
- Avoid strong CYP3A4 inducers as they can decrease the plasma exposure to XTANDI. If co-administration is necessary, increase the dose of XTANDI. (2.2, 7.2)
- Avoid CYP3A4, CYP2C9 and CYP2C19 substrates with a narrow therapeutic index, as XTANDI may decrease the plasma exposures of these drugs. If XTANDI is co-administered with warfarin (CYP2C9 substrate), conduct additional INR monitoring. (7.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

XTANDI® is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC).

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of XTANDI is 160 mg (four 40 mg capsules) administered orally once daily. XTANDI can be taken with or without food *[see Clinical Pharmacology (12.3)]*. Swallow capsules whole. Do not chew, dissolve, or open the capsules.

2.2 Dose Modifications

If a patient experiences a ≥ Grade 3 toxicity or an intolerable side effect, withhold dosing for one week or until symptoms improve to ≤ Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg), if warranted.

Concomitant Strong CYP2C8 Inhibitors

The concomitant use of strong CYP2C8 inhibitors should be avoided if possible. If patients must be co-administered a strong CYP2C8 inhibitor, reduce the XTANDI dose to 80 mg once daily. If co-administration of the strong inhibitor is discontinued, the XTANDI dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

Concomitant Strong CYP3A4 Inducers

The concomitant use of strong CYP3A4 inducers should be avoided if possible. If patients must be co-administered a strong CYP3A4 inducer, increase the XTANDI dose from 160 mg to 240 mg once daily. If co-administration of the strong CYP3A4 inducer is discontinued, the XTANDI dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

XTANDI 40 mg capsules are white to off-white oblong soft gelatin capsules imprinted in black ink with ENZ.

4 CONTRAINDICATIONS

Pregnancy

XTANDI can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. XTANDI is not indicated for use in women. XTANDI is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss *[see Use in Specific Populations (8.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Seizure

In Study 1, which enrolled patients who previously received docetaxel, 7 of 800 (0.9%) patients treated with XTANDI experienced a seizure and no patients treated with placebo experienced a seizure. Seizure occurred from 31 to 603 days after initiation of XTANDI. In Study 2, 1 of 871 (0.1%) chemotherapy-naive patients treated with XTANDI and 1 of 844 (0.1%) patients treated with placebo experienced a seizure. Patients experiencing seizure were permanently discontinued from therapy and all seizure events resolved. There is no clinical trial experience re-administering XTANDI to patients who experienced seizure.

Limited safety data are available in patients with predisposing factors for seizure because these patients were generally excluded from the trials. 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, and brain arteriovenous malformation. Study 1 excluded the use of concomitant medications that may lower the seizure threshold, whereas Study 2 permitted the use of these medications.

Because of the risk of seizure associated with XTANDI 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. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

5.2 Posterior Reversible Encephalopathy Syndrome (PRES)
There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving XTANDI *[see Adverse Reactions (6.2)]*. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue XTANDI in patients who develop PRES.

6 ADVERSE REACTIONS
The following is discussed in more detail in other sections of the labeling:

- Seizure *[see Warnings and Precautions (5.1)]*
- Posterior Reversible Encephalopathy Syndrome (PRES) *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Two randomized clinical trials enrolled patients with metastatic prostate cancer that has progressed on androgen deprivation therapy (GnRH therapy or bilateral orchiectomy), a disease setting that is also defined as metastatic CRPC. In both studies, patients received XTANDI 160 mg orally once daily in the active treatment arm or placebo in the control arm. All patients continued androgen deprivation therapy. Patients were allowed, but not required, to take glucocorticoids.

The most common adverse reactions (≥ 10%) that occurred more commonly (≥ 2% over placebo) in the XTANDI-treated patients from the two randomized clinical trials were asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo.

Study 1: Metastatic Castration-Resistant Prostate Cancer Following Chemotherapy
Study 1 enrolled 1199 patients with metastatic CRPC who had previously received docetaxel. The median duration of treatment was 8.3 months with XTANDI and 3.0 months with placebo. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids.

Grade 3 and higher adverse reactions were reported among 47% of XTANDI-treated patients and 53% of placebo-treated patients. Discontinuations due to adverse events were reported for 16% of XTANDI-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 XTANDI-treated patients compared to none (0%) of the placebo-treated patients. Table 1 shows adverse reactions reported in Study 1 that occurred at a ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

Table 1. Adverse Reactions in Study 1

	XTANDI N = 800		Placebo N = 399	
	Grade 1-4[a] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
General Disorders				
Asthenic Conditions[b]	50.6	9.0	44.4	9.3
Peripheral Edema	15.4	1.0	13.3	0.8
Musculoskeletal And Connective Tissue Disorders				
Back Pain	26.4	5.3	24.3	4.0
Arthralgia	20.5	2.5	17.3	1.8
Musculoskeletal Pain	15.0	1.3	11.5	0.3
Muscular Weakness	9.8	1.5	6.8	1.8
Musculoskeletal Stiffness	2.6	0.3	0.3	0.0
Gastrointestinal Disorders				
Diarrhea	21.8	1.1	17.5	0.3
Vascular Disorders				
Hot Flush	20.3	0.0	10.3	0.0
Hypertension	6.4	2.1	2.8	1.3
Nervous System Disorders				
Headache	12.1	0.9	5.5	0.0
Dizziness[c]	9.5	0.5	7.5	0.5
Spinal Cord Compression and Cauda Equina Syndrome	7.4	6.6	4.5	3.8
Paresthesia	6.6	0.0	4.5	0.0
Mental Impairment Disorders[d]	4.3	0.3	1.8	0.0
Hypoesthesia	4.0	0.3	1.8	0.0
Infections And Infestations				
Upper Respiratory Tract Infection[e]	10.9	0.0	6.5	0.3
Lower Respiratory Tract And Lung Infection[f]	8.5	2.4	4.8	1.3
Psychiatric Disorders				
Insomnia	8.8	0.0	6.0	0.5
Anxiety	6.5	0.3	4.0	0.0
Renal And Urinary Disorders				
Hematuria	6.9	1.8	4.5	1.0
Pollakiuria	4.8	0.0	2.5	0.0
Injury, Poisoning And Procedural Complications				
Fall	4.6	0.3	1.3	0.0
Non-pathologic Fractures	4.0	1.4	0.8	0.3
Skin And Subcutaneous Tissue Disorders				
Pruritus	3.8	0.0	1.3	0.0
Dry Skin	3.5	0.0	1.3	0.0

	XTANDI N = 800		Placebo N = 399	
	Grade 1-4[a] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Respiratory Disorders				
Epistaxis	3.3	0.1	1.3	0.3

a CTCAE v4
b Includes asthenia and fatigue.
c Includes dizziness and vertigo.
d Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.
e Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.
f Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection.

Study 2: Chemotherapy-naive Metastatic Castration-Resistant Prostate Cancer

Study 2 enrolled 1717 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 1715 received at least one dose of study drug. The median duration of treatment was 17.5 months with XTANDI and 4.6 months with placebo. Grade 3-4 adverse reactions were reported in 44% of XTANDI-treated patients and 37% of placebo-treated patients. Discontinuations due to adverse events were reported for 6% of XTANDI-treated patients and 6% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was fatigue/asthenia, which occurred in 1% of patients on each treatment arm. Table 2 includes adverse reactions reported in Study 2 that occurred at a ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

Table 2. Adverse Reactions in Study 2

	XTANDI N = 871		Placebo N = 844	
	Grade 1-4[a] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
General Disorders				
Asthenic Conditions[b]	46.9	3.4	33.0	2.8
Peripheral Edema	11.5	0.2	8.2	0.4
Musculoskeletal And Connective Tissue Disorders				
Back Pain	28.6	2.5	22.4	3.0
Arthralgia	21.4	1.6	16.1	1.1
Gastrointestinal Disorders				
Constipation	23.2	0.7	17.3	0.4
Diarrhea	16.8	0.3	14.3	0.4
Vascular Disorders				
Hot Flush	18.0	0.1	7.8	0.0
Hypertension	14.2	7.2	4.1	2.3
Nervous System Disorders				
Dizziness[c]	11.3	0.3	7.1	0.0
Headache	11.0	0.2	7.0	0.4
Dysgeusia	7.6	0.1	3.7	0.0
Mental Impairment Disorders[d]	5.7	0.0	1.3	0.1
Restless Legs Syndrome	2.1	0.1	0.4	0.0
Respiratory Disorders				
Dyspnea[e]	11.0	0.6	8.5	0.6
Infections And Infestations				
Upper Respiratory Tract	16.4	0.0	10.5	0.0

	XTANDI N = 871		Placebo N = 844	
	Grade 1-4[a] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Infection[f]				
Lower Respiratory Tract And Lung Infection[g]	7.9	1.5	4.7	1.1
Psychiatric Disorders				
Insomnia	8.2	0.1	5.7	0.0
Renal And Urinary Disorders				
Hematuria	8.8	1.3	5.8	1.3
Injury, Poisoning And Procedural Complications				
Fall	12.7	1.6	5.3	0.7
Non-Pathological Fracture	8.8	2.1	3.0	1.1
Metabolism and Nutrition Disorders				
Decreased Appetite	18.9	0.3	16.4	0.7
Investigations				
Weight Decreased	12.4	0.8	8.5	0.2
Reproductive System and Breast disorders				
Gynecomastia	3.4	0.0	1.4	0.0

a CTCAE v4
b Includes asthenia and fatigue.
c Includes dizziness and vertigo.
d Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.
e Includes dyspnea, exertional dyspnea, and dyspnea at rest.
f Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.
g Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection.

Laboratory Abnormalities
In the two randomized clinical trials, Grade 1-4 neutropenia occurred in 15% of patients treated with XTANDI (1% Grade 3-4) and in 6% of patients treated with placebo (0.5% Grade 3-4). The incidence of Grade 1-4 thrombocytopenia was 6% of patients treated with XTANDI (0.3% Grade 3-4) and 5% of patients treated with placebo (0.5% Grade 3-4). Grade 1-4 elevations in ALT occurred in 10% of patients treated with XTANDI (0.2% Grade 3-4) and 16% of patients treated with placebo (0.2% Grade 3-4). Grade 1-4 elevations in bilirubin occurred in 3% of patients treated with XTANDI (0.1% Grade 3-4) and 2% of patients treated with placebo (no Grade 3-4).

Infections
In Study 1, 1% of patients treated with XTANDI compared to 0.3% of patients treated with placebo died from infections or sepsis. In Study 2, 1 patient in each treatment group (0.1%) had an infection resulting in death.

Falls and Fall-related Injuries
In the two randomized clinical trials, falls including fall-related injuries, occurred in 9% of patients treated with XTANDI compared to 4% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in patients treated with XTANDI and included non-pathologic fractures, joint injuries, and hematomas.

Hypertension
In the two randomized trials, hypertension was reported in 11% of patients receiving XTANDI and 4% of patients receiving placebo. No patients experienced hypertensive crisis. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in < 1% of patients in each arm.

6.2 Post-Marketing Experience
The following additional adverse reactions have been identified during post approval use of XTANDI. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Neurological Disorders: posterior reversible encephalopathy syndrome (PRES)

7 DRUG INTERACTIONS

7.1 Drugs that Inhibit CYP2C8
Co-administration of a strong CYP2C8 inhibitor (gemfibrozil) increased the composite area under the plasma concentration-time curve (AUC) of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold. Co-administration of XTANDI with strong CYP2C8 inhibitors should be avoided if possible. If co-administration of XTANDI with a strong CYP2C8 inhibitor cannot be avoided, reduce the dose of XTANDI *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

7.2 Drugs that Induce CYP3A4
Co-administration of rifampin (strong CYP3A4 inducer and moderate CYP2C8 inducer) decreased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 37%. Co-administration of strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) with XTANDI should be avoided if possible. St John's wort may decrease enzalutamide exposure and should be avoided. If co-administration of a strong CYP3A4 inducer with XTANDI cannot be avoided, increase the dose of XTANDI *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

7.3 Effect of XTANDI on Drug Metabolizing Enzymes
Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. At steady state, XTANDI reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). Concomitant use of XTANDI 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) and CYP2C19 (e.g., S-mephenytoin) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category X *[see Contraindications (4)]*.

Risk Summary
XTANDI can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. While there are no human data on the use of XTANDI in pregnancy and XTANDI is not indicated for use in women, it is important to know that maternal use of an androgen receptor inhibitor could affect development of the fetus. Enzalutamide caused embryo-fetal toxicity in mice at exposures that were lower than in patients receiving the recommended dose. XTANDI is contraindicated in women who are or may become pregnant while receiving the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss. Advise females of reproductive potential to avoid becoming pregnant during treatment with XTANDI.

Animal Data
In an embryo-fetal developmental toxicity study in mice, enzalutamide caused developmental toxicity when administered at oral doses of 10 or 30 mg/kg/day throughout the period of organogenesis (gestational days 6-15). Findings included embryo-fetal lethality (increased post-implantation loss and resorptions) and decreased anogenital distance at ≥ 10 mg/kg/day, and cleft palate and absent palatine bone at 30 mg/kg/day. Doses of 30 mg/kg/day caused maternal toxicity. The doses tested in mice (1, 10 and 30 mg/kg/day) resulted in systemic exposures (AUC) approximately 0.04, 0.4 and 1.1 times, respectively, the exposures in patients. Enzalutamide did not cause developmental toxicity in rabbits when administered throughout the period of organogenesis (gestational days 6-18) at dose levels up to 10 mg/kg/day (approximately 0.4 times the exposures in patients based on AUC).

8.3 Nursing Mothers
XTANDI is not indicated for use in women. It is not known if enzalutamide is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from XTANDI, a decision should be made to either discontinue nursing, or discontinue the drug taking into account the importance of the drug to the mother.

8.4 Pediatric Use
Safety and effectiveness of XTANDI in pediatric patients have not been established.

8.5 Geriatric Use
Of 1671 patients who received XTANDI in the two randomized clinical trials, 75% were 65 and over, while 31% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Patients with Renal Impairment
A dedicated renal impairment trial for XTANDI has not been conducted. Based on the population pharmacokinetic analysis using data from clinical trials in patients with metastatic CRPC and healthy volunteers, no significant difference in enzalutamide clearance was observed in patients with pre-existing mild to moderate renal impairment (30 mL/min ≤ creatinine clearance [CrCL] ≤ 89 mL/min) compared to patients and volunteers with baseline normal renal function (CrCL ≥ 90 mL/min). No initial dosage adjustment is necessary for patients with mild to moderate renal impairment. Severe renal impairment (CrCL < 30 mL/min) and end-stage renal disease have not been assessed *[see Clinical Pharmacology (12.3)]*.

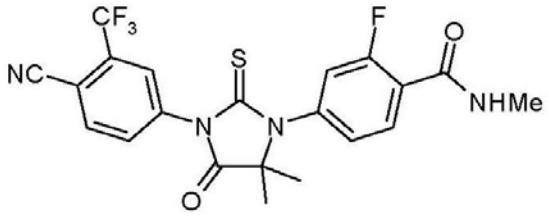
8.7 Patients with Hepatic Impairment
Dedicated hepatic impairment trials compared the composite systemic exposure of enzalutamide plus N-desmethyl enzalutamide in volunteers with baseline mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C, respectively) versus healthy controls with normal hepatic function. The composite AUC of enzalutamide plus N-desmethyl enzalutamide was similar in volunteers with mild, moderate, or severe baseline hepatic impairment compared to volunteers with normal hepatic function. No initial dosage adjustment is necessary for patients with baseline mild, moderate, or severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE
In the event of an overdose, stop treatment with XTANDI and initiate general supportive measures taking into consideration the half-life of 5.8 days. In a dose escalation study, no seizures were reported at ≤ 240 mg daily, whereas 3 seizures were reported, 1 each at 360 mg, 480 mg, and 600 mg daily. Patients may be at increased risk of seizure following an overdose.

11 DESCRIPTION

Enzalutamide 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}-2-fluoro-*N*-methylbenzamide.

The molecular weight is 464.44 and molecular formula is $C_{21}H_{16}F_4N_4O_2S$. The structural formula is:



Enzalutamide is a white crystalline non-hygroscopic solid. It is practically insoluble in water.

XTANDI is provided as liquid-filled soft gelatin capsules for oral administration. Each capsule contains 40 mg of enzalutamide as a solution 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Enzalutamide is an androgen receptor inhibitor that acts on different steps in the androgen receptor signaling pathway. Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors and inhibit androgen receptor nuclear translocation and interaction with DNA. A major metabolite, N-desmethyl enzalutamide, exhibited similar *in vitro* activity to enzalutamide. Enzalutamide decreased proliferation and induced cell death of prostate cancer cells *in vitro*, and decreased tumor volume in a mouse prostate cancer xenograft model.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of enzalutamide 160 mg/day at steady state on the QTc interval was evaluated in 796 patients with metastatic CRPC. No large difference (i.e., greater than 20 ms) was observed between the mean QT interval change from baseline in patients treated with XTANDI and that in patients treated with placebo, based on the Fridericia correction method. However, small increases in the mean QTc interval (i.e., less than 10 ms) due to enzalutamide cannot be excluded due to limitations of the study design.

12.3 Pharmacokinetics

The pharmacokinetics of enzalutamide and its major active metabolite (N-desmethyl enzalutamide) were evaluated in patients with metastatic CRPC and healthy male volunteers. The plasma enzalutamide pharmacokinetics are adequately described by a linear two-compartment model with first-order absorption.

Absorption

Following oral administration (XTANDI 160 mg daily) in patients with metastatic CRPC, the median time to reach maximum plasma enzalutamide concentrations (C_{max}) is 1 hour (range 0.5 to 3 hours). At steady state, the plasma mean C_{max} values for enzalutamide and N-desmethyl enzalutamide are 16.6 µg/mL (23% CV) and 12.7 µg/mL (30% CV), respectively, and the plasma mean predose trough values are 11.4 µg/mL (26% CV) and 13.0 µg/mL (30% CV), respectively.

With the daily dosing regimen, enzalutamide steady state is achieved by Day 28, and enzalutamide accumulates approximately 8.3-fold relative to a single dose. Daily fluctuations in enzalutamide plasma concentrations are low (mean peak-to-trough ratio of 1.25). At steady state, enzalutamide showed approximately dose proportional pharmacokinetics over the daily dose range of 30 to 360 mg.

A single 160 mg oral dose of XTANDI was administered to healthy volunteers with a high-fat meal or in the fasted condition. A high-fat meal did not alter the AUC to enzalutamide or N-desmethyl enzalutamide. The results are summarized in Figure 1.

Distribution and Protein Binding
The mean apparent volume of distribution (V/F) of enzalutamide in patients after a single oral dose is 110 L (29% CV).

Enzalutamide is 97% to 98% bound to plasma proteins, primarily albumin. N-desmethyl enzalutamide is 95% bound to plasma proteins. *In vitro*, there was no protein binding displacement between enzalutamide and other highly protein bound drugs (warfarin, ibuprofen, and salicylic acid) at clinically relevant concentrations.

Metabolism
Following single oral administration of ^{14}C-enzalutamide 160 mg, plasma samples were analyzed for enzalutamide and its metabolites up to 77 days post dose. Enzalutamide, N-desmethyl enzalutamide, and a major inactive carboxylic acid metabolite accounted for 88% of the ^{14}C-radioactivity in plasma, representing 30%, 49%, and 10%, respectively, of the total ^{14}C-$AUC_{0\text{-}inf}$.

In vitro, human CYP2C8 and CYP3A4 are responsible for the metabolism of enzalutamide. Based on *in vivo* and *in vitro* data, CYP2C8 is primarily responsible for the formation of the active metabolite (N-desmethyl enzalutamide).

In vitro, N-desmethyl enzalutamide is not a substrate of human CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5.

Elimination
Enzalutamide is primarily eliminated by hepatic metabolism. Following single oral administration of ^{14}C-enzalutamide 160 mg, 85% of the radioactivity is recovered by 77 days post dose: 71% is recovered in urine (including only trace amounts of enzalutamide and N-desmethyl enzalutamide), and 14% is recovered in feces (0.4% of dose as unchanged enzalutamide and 1% as N-desmethyl enzalutamide).

The mean apparent clearance (CL/F) of enzalutamide in patients after a single oral dose is 0.56 L/h (range 0.33 to 1.02 L/h).

The mean terminal half-life ($t_{1/2}$) for enzalutamide in patients after a single oral dose is 5.8 days (range 2.8 to 10.2 days). Following a single 160 mg oral dose of enzalutamide in healthy volunteers, the mean terminal $t_{1/2}$ for N-desmethyl enzalutamide is approximately 7.8 to 8.6 days.

Pharmacokinetics in Special Populations
Renal Impairment:
A population pharmacokinetic analysis (based on pre-existing renal function) was carried out with data from 59 healthy male volunteers and 926 patients with metastatic CRPC enrolled in clinical trials, including 512 with normal renal function (CrCL ≥ 90 mL/min), 332 with mild renal impairment (CrCL 60 to < 90 mL/min), 88 with moderate renal impairment (CrCL 30 to < 60 mL/min), and 1 with severe renal impairment (CrCL < 30 mL/min). The apparent clearance of enzalutamide was similar in patients with pre-existing mild and moderate renal impairment (CrCL 30 to < 90 mL/min) compared to patients and volunteers with normal renal function. The potential effect of severe renal

impairment or end stage renal disease on enzalutamide pharmacokinetics cannot be determined as clinical and pharmacokinetic data are available from only one patient *[see Use in Specific Populations (8.6)]*.

Hepatic Impairment:
The plasma pharmacokinetics of enzalutamide and N-desmethyl enzalutamide were examined in volunteers with normal hepatic function (N = 22) and with pre-existing mild (N = 8, Child-Pugh Class A) moderate (N = 8, Child-Pugh B), or severe (N = 8, Child-Pugh C) hepatic impairment. XTANDI was administered as a single 160 mg dose. The composite AUC of enzalutamide plus N-desmethyl enzalutamide was similar in volunteers with mild, moderate, or severe baseline hepatic impairment compared to volunteers with normal hepatic function. The results are summarized in Figure 1 *[see Use in Specific Populations (8.7)]*.

Body Weight and Age:
Population pharmacokinetic analyses showed that weight (range: 46 to 163 kg) and age (range: 41 to 92 yr) do not have a clinically meaningful influence on the exposure to enzalutamide.

Gender:
The effect of gender on the pharmacokinetics of enzalutamide has not been evaluated.

Race:
The majority of XTANDI-treated patients in the randomized clinical trials were Caucasian (85%). Based on pharmacokinetic data from a study in Japanese patients with prostate cancer, there were no clinically relevant differences in exposure between Japanese and Caucasians. There are insufficient data to evaluate potential differences in the pharmacokinetics of enzalutamide in other races.

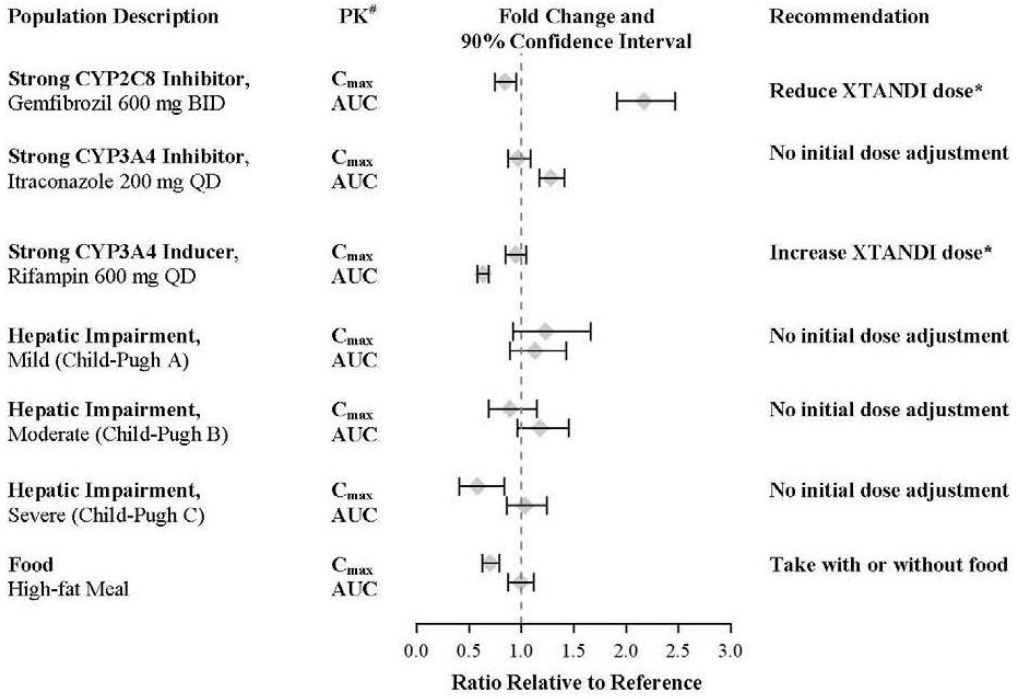
Drug Interactions

Effect of Other Drugs on XTANDI:
In a drug-drug interaction trial in healthy volunteers, a single 160 mg oral dose of XTANDI was administered alone or after multiple oral doses of gemfibrozil (strong CYP2C8 inhibitor). Gemfibrozil increased the $AUC_{0\text{-}inf}$ of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold with minimal effect on C_{max}. The results are summarized in Figure 1 *[see Dosage and Administration (2.2) and Drug Interactions (7.1)]*.

In a drug-drug interaction trial in healthy volunteers, a single 160 mg oral dose of XTANDI was administered alone or after multiple oral doses of rifampin (strong CYP3A4 and moderate CYP2C8 inducer). Rifampin decreased the $AUC_{0\text{-}inf}$ of enzalutamide plus N-desmethyl enzalutamide by 37% with no effect on C_{max}. The results are summarized in Figure 1 *[see Dosage and Administration (2.2) and Drug Interactions (7.2)]*.

In a drug-drug interaction trial in healthy volunteers, a single 160 mg oral dose of XTANDI was administered alone or after multiple oral doses of itraconazole (strong CYP3A4 inhibitor). Itraconazole increased the $AUC_{0\text{-}inf}$ of enzalutamide plus N-desmethyl enzalutamide by 1.3-fold with no effect on C_{max}. The results are summarized in Figure 1.

Figure 1. Effects of Other Drugs and Intrinsic/Extrinsic Factors on XTANDI



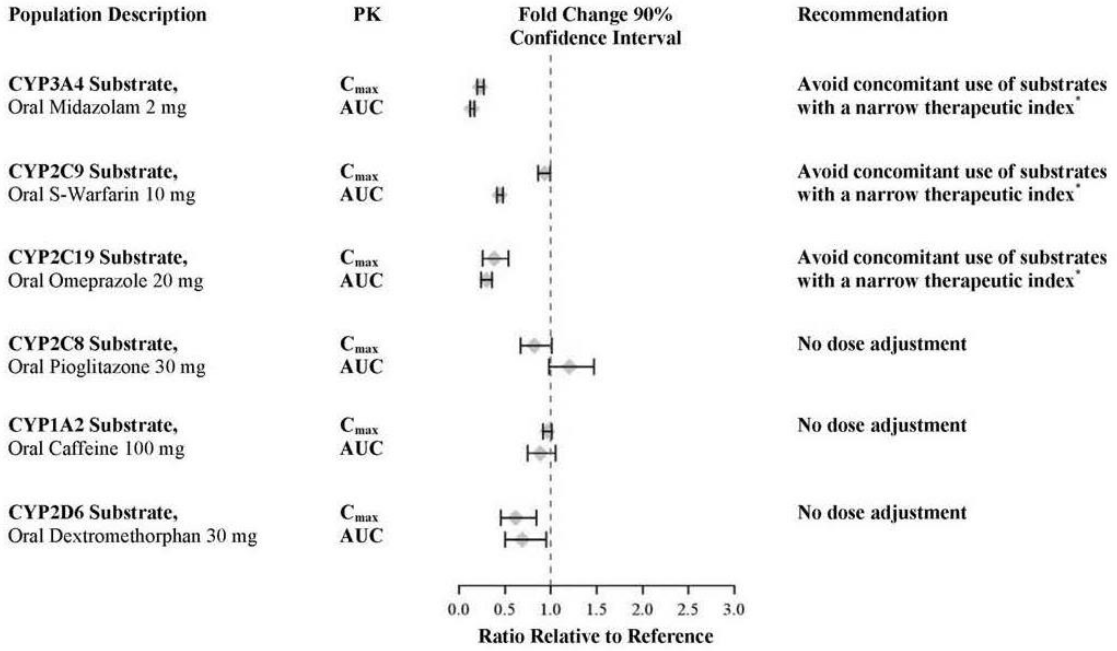
PK parameters (C_{max} and $AUC_{0\text{-}inf}$) are for enzalutamide plus N-desmethyl enzalutamide, except in the food-effect trial, where they are for enzalutamide alone.
* See Dosage and Administration (2.2).

Effect of XTANDI on Other Drugs:

In an *in vivo* phenotypic cocktail drug-drug interaction trial in patients with metastatic CRPC, a single oral dose of the CYP probe substrate cocktail (for CYP2C8, CYP2C9, CYP2C19, and CYP3A4) was administered before and concomitantly with XTANDI (following at least 55 days of dosing at 160 mg daily). The results are summarized in Figure 2. Results showed that *in vivo*, at steady state, XTANDI is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer *[see Drug Interactions (7.3)]*. XTANDI did not cause clinically meaningful changes in exposure to the CYP2C8 substrate.

In an *in vivo* phenotypic cocktail drug-drug interaction trial in patients with CRPC, a single oral dose of the CYP probe substrate cocktail for CYP1A2 and CYP2D6 was administered before and concomitantly with XTANDI (following at least 49 days of dosing at 160 mg daily). The results are summarized in Figure 2. Results showed that *in vivo*, at steady state, XTANDI did not cause clinically meaningful changes in exposure to the CYP1A2 or CYP2D6 substrates.

Figure 2. Effect of XTANDI on Other Drugs



*See Drug Interactions (7.3).

In vitro, enzalutamide, N-desmethyl enzalutamide, and the major inactive carboxylic acid metabolite caused direct inhibition of multiple CYP enzymes including CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5; however, subsequent clinical data showed that XTANDI is an inducer of CYP2C9, CYP2C19, and CYP3A4 and had no clinically meaningful effect on CYP2C8 (see Figure 2). *In vitro*, enzalutamide caused time-dependent inhibition of CYP1A2.

In vitro studies showed that enzalutamide induces CYP2B6 and CYP3A4 and does not induce CYP1A2 at therapeutically relevant concentrations.

In vitro, enzalutamide, N-desmethyl enzalutamide, and the major inactive carboxylic acid metabolite are not substrates for human P-glycoprotein. *In vitro*, enzalutamide and N-desmethyl enzalutamide are inhibitors of human P-glycoprotein, while the major inactive carboxylic acid metabolite is not.

In vitro, enzalutamide and N-desmethyl enzalutamide do not appear to be substrates of human breast cancer resistance protein (BCRP); however, enzalutamide and N-desmethyl enzalutamide are inhibitors of human BCRP at clinically relevant concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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* mouse lymphoma thymidine kinase (Tk) gene mutation assay or the *in vivo* mouse micronucleus assay.

Based on nonclinical findings in repeat-dose toxicology studies, which were consistent with the pharmacological activity of enzalutamide, male fertility may be impaired by treatment with XTANDI. In a 26-week study in rats, atrophy of the prostate and seminal vesicles was observed at ≥ 30 mg/kg/day (equal to the human exposure based on AUC). In 4-, 13-, and 39-week studies in dogs, hypospermatogenesis and atrophy of the prostate and epididymides were observed at ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC).

14 CLINICAL STUDIES

The efficacy and safety of XTANDI in patients with metastatic CRPC were demonstrated in two randomized, placebo-controlled, multicenter phase 3 clinical trials. All patients continued on GnRH therapy or had prior bilateral orchiectomy. Patients were allowed, but not required, to continue or initiate glucocorticoids.

Study 1: Metastatic Castration-Resistant Prostate Cancer Following Chemotherapy

A total of 1199 patients who had received prior docetaxel-based chemotherapy were randomized 2:1 to receive either XTANDI orally at a dose of 160 mg once daily (N=800) or placebo orally once daily (N=399). Study treatment continued until disease progression (evidence of radiographic progression, a skeletal-related event, or clinical progression), initiation of new systemic antineoplastic treatment, unacceptable toxicity, or withdrawal. Patients with a previous history of seizure, taking medicines known to decrease the seizure threshold, or with other risk factors for seizure were not eligible *[see Warnings and Precautions (5.1)]*.

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 69 years (range 41-92) and the racial distribution was 92.7% Caucasian, 3.9% Black, 1.1% Asian, and 2.1% Other. Ninety-two percent of patients had an ECOG performance status score of 0-1 and 28% had a mean Brief Pain Inventory score of ≥ 4. Ninety-one percent of patients had metastases in bone and 23% had visceral involvement in the lung and/or liver. Fifty-nine percent of patients had radiographic evidence of disease progression and 41% had PSA-only progression on study entry. All patients had received prior docetaxel-based therapy and 24% had received two cytotoxic chemotherapy regimens. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids.

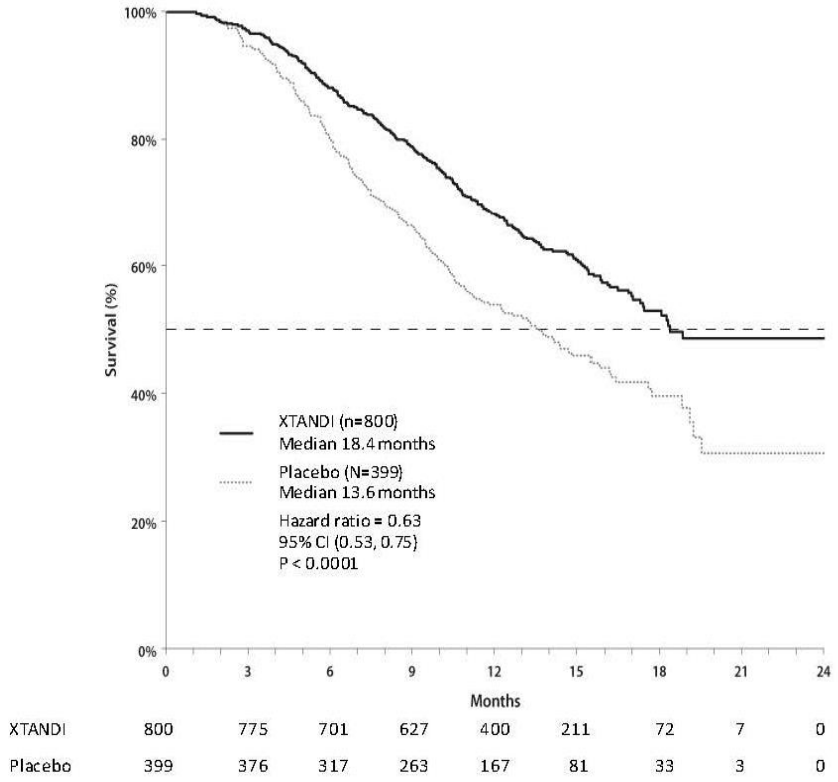
A statistically significant improvement in overall survival was demonstrated at the pre-specified interim analysis at the time of 520 deaths in patients on the XTANDI arm compared to patients on the placebo arm (Table 3 and Figure 3).

Table 3. Overall Survival of Patients Treated with Either XTANDI or Placebo in Study 1

	XTANDI N = 800	Placebo N = 399
Number of Deaths (%)	308 (38.5%)	212 (53.1%)
Median Survival, months (95% CI)	18.4 (17.3, NR)	13.6 (11.3, 15.8)
P-value[a]	< 0.0001	
Hazard Ratio (95% CI)[b]	0.63 (0.53, 0.75)	

a) P-value is derived from a log-rank test stratified by baseline ECOG performance status score (0-1 vs. 2) and mean baseline pain score (BPI-SF score < 4 vs. ≥ 4)
b) Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors XTANDI
NR denotes "not reached".

Figure 3. Kaplan-Meier Overall Survival Curves in Study 1



Study 2: Chemotherapy-naive Metastatic Castration-Resistant Prostate Cancer

In Study 2, 1717 chemotherapy-naive patients were randomized 1:1 to receive either XTANDI orally at a dose of 160 mg once daily (N=872) or placebo orally once daily (N=845). Patients with visceral metastases, patients with a history of mild to moderate heart failure (NYHA class I or II), and patients taking medications associated with lowering the seizure threshold were allowed. Patients with a previous history of seizure or a condition that might predispose to seizure and patients with moderate or severe pain from prostate cancer were excluded. Study treatment continued until disease progression (evidence of radiographic progression, a skeletal-related event, or clinical

progression) and the initiation of a cytotoxic chemotherapy or an investigational agent, unacceptable toxicity, or withdrawal. Overall survival and radiographic progression-free survival (rPFS) were assessed. Radiographic progression was assessed with the use of sequential imaging and was defined by bone scan identification of 2 or more new bone lesions with confirmation (Prostate Cancer Clinical Trials Working Group 2 criteria) and/or Response Evaluation Criteria in Solid Tumors (RECIST v 1.1) criteria for progression of soft tissue lesions. The primary analysis of rPFS utilized centrally reviewed radiographic assessment of progression.

Patient demographics and baseline disease characteristics were balanced between the treatment arms at entry. The median age was 71 years (range 42-93) and the racial distribution was 77% Caucasian, 10% Asian, 2% Black and 11% Other. The ECOG performance status score was 0 for 68% of patients, and 1 for 32% of patients. Baseline pain assessment was 0-1 (asymptomatic) in 67% of patients, and 2-3 (mildly symptomatic) in 32% of patients as defined by the Brief Pain Inventory Short Form (worst pain over past 24 hours at study entry). Fifty-four percent of patients had radiographic evidence of disease progression and 43% had PSA-only progression. Twelve percent of patients had visceral (lung and/or liver) disease involvement. During the study, 27% of patients on the XTANDI arm and 30% of patients on the placebo arm received glucocorticoids for varying reasons.

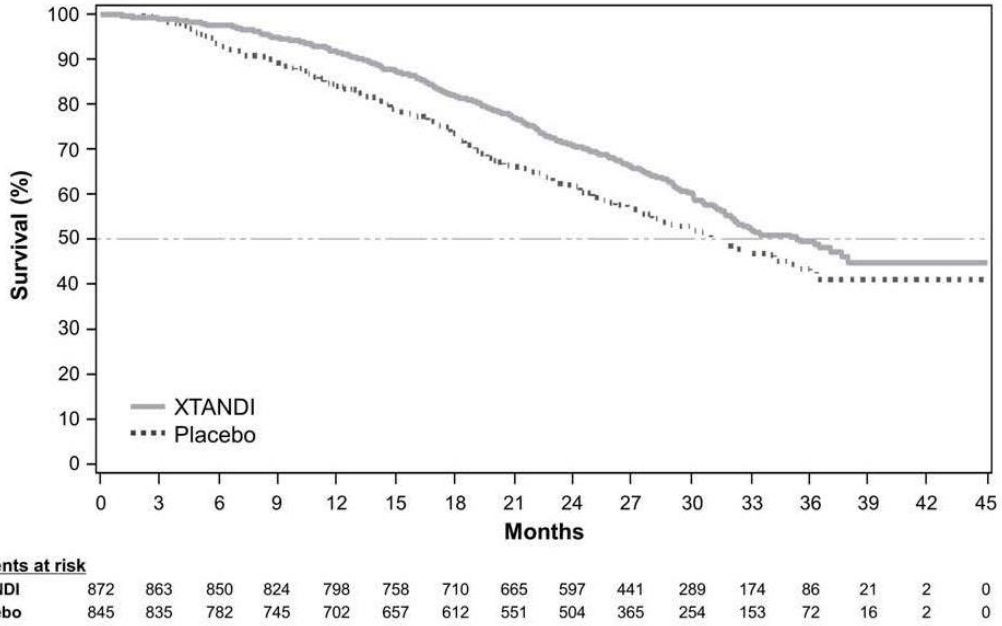
A statistically significant improvement in overall survival was demonstrated at the pre-specified interim analysis, conducted after 540 deaths in patients treated with XTANDI compared to those treated with placebo (Table 4). Forty percent of XTANDI-treated and 70% of placebo-treated patients received subsequent therapies for metastatic CRPC that may prolong overall survival. An updated survival analysis was conducted when 784 deaths were observed. The median follow-up time was 31 months. Results from this analysis were consistent with those from the pre-specified interim analysis (Table 4, Figure 4). At the updated analysis, 52% of XTANDI-treated and 81% of placebo-treated patients had received subsequent therapies that may prolong overall survival in metastatic CRPC. XTANDI was used as a subsequent therapy in 2% of XTANDI-treated patients and 29% of placebo-treated patients.

Table 4. Overall Survival of Patients Treated with Either XTANDI or Placebo in Study 2

	XTANDI N = 872	Placebo N = 845
Pre-specified Interim Analysis[a]		
Number of Deaths (%)	241 (28%)	299 (35%)
Median Survival, months (95% CI)	32.4 (30.1, NR)	30.2 (28.0, NR)
P-value[b]	< 0.0001	
Hazard Ratio (95% CI)[c]	0.71 (0.60, 0.84)	
Updated Survival Analysis[d]		
Number of Deaths (%)	368 (42%)	416 (49%)
Median Survival, months (95% CI)	35.3 (32.2, NR)	31.3 (28.8, 34.2)
Hazard Ratio (95% CI)[c]	0.77 (0.67, 0.88)	

[a] The data cutoff date is 16 Sep 2013
[b] P-value is derived from an unstratified log-rank test.
[c] Hazard ratio is derived from an unstratified proportional hazards model. Hazard ratio < 1 favors XTANDI.
[d] The data cutoff date is 1 Jun 2014. The planned number of deaths for the final overall survival analysis was ≥765.
NR denotes "not reached".

Figure 4. Kaplan-Meier Overall Survival Curves in Study 2



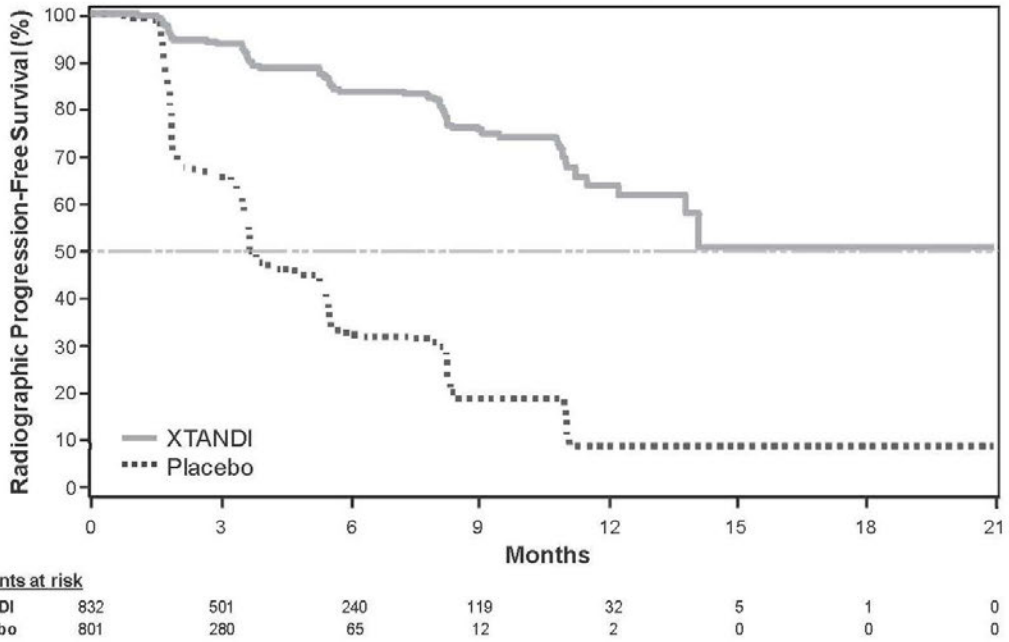
A statistically significant improvement in rPFS was demonstrated in patients treated with XTANDI compared to patients treated with placebo (Table 5, Figure 5).

Table 5. Radiographic Progression-free Survival of Patients Treated with Either XTANDI or Placebo in Study 2

	XTANDI N = 832	Placebo N = 801
Number of Progression or Deaths (%)	118 (14%)	320 (40%)
Median rPFS (months) (95% CI)	NR (13.8, NR)	3.7 (3.6, 4.6)
P-value[a]	< 0.0001	
Hazard Ratio (95% CI)[b]	0.17 (0.14, 0.21)	

[a] P-value is derived from an unstratified log-rank test
[b] Hazard Ratio is derived from an unstratified proportional hazards model. Hazard ratio <1 favors XTANDI
NR denotes "not reached".
Note: As of the cutoff date for the rPFS analysis, 1633 patients had been randomized.

Figure 5. Kaplan-Meier Curves for Duration of Radiographic Progression-free Survival in Study 2



Patients at risk

XTANDI	832	501	240	119	32	5	1	0
Placebo	801	280	65	12	2	0	0	0

Time to initiation of cytotoxic chemotherapy was prolonged after XTANDI treatment, with a median of 28.0 months for patients on the XTANDI arm versus a median of 10.8 months for patients on the placebo arm [HR=0.35 (95% CI: 0.30, 0.40), $p < 0.0001$].

The median time to first skeletal-related event was 31.1 months for patients on the XTANDI arm versus 31.3 months for patients on the placebo arm [HR = 0.72 (95% CI: 0.61, 0.84), $p < 0.0001$]. A skeletal-related event was defined as radiation therapy or surgery to bone for prostate cancer, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain.

16 HOW SUPPLIED/STORAGE AND HANDLING

- XTANDI (enzalutamide) 40 mg capsules are supplied as white to off-white oblong soft gelatin capsules imprinted in black ink with ENZ. XTANDI capsules are available in the following package sizes:
  - Bottles of 120 capsules (NDC 0469-0125-99)

Recommended storage: Store XTANDI capsules at 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).

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (PATIENT INFORMATION).

- Instruct patients to take their dose at the same time each day (once daily). XTANDI can be taken with or without food. Each capsule should be swallowed whole. Do not chew, dissolve, or open the capsules.
- Inform patients receiving GnRH therapy that they need to maintain this treatment during the course of treatment with XTANDI.

- Inform patients that XTANDI has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Inform patients to contact their physician right away if they have loss of consciousness or seizure.
- Inform patients to contact their physician right away if they experience rapidly worsening symptoms possibly indicative of PRES such as seizure, headache, decreased alertness, confusion, reduced eyesight, or blurred vision.
- Inform patients that they should not interrupt, modify the dose, or stop XTANDI without first consulting their physician. Inform patients that if they miss a dose, then they should take it as soon as they remember. If they forget to take the dose for the whole day, then they should take their normal dose the next day. They should not take more than their prescribed dose per day.
- Apprise patients of the most common side effects associated with XTANDI: asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Inform patients that XTANDI may cause infections, falls and fall-related injuries, and hypertension.
- Inform patients that XTANDI can be harmful to a developing fetus. Patients should also be informed that they should use a condom if having sex with a pregnant woman. A condom and another effective method of birth control should be used if the patient is having sex with a woman of child-bearing potential. These measures are required during and for three months after treatment with XTANDI.

Manufactured by: Catalent Pharma Solutions, LLC, St. Petersburg, FL 33716
Manufactured for and Distributed by: Astellas Pharma US, Inc., Northbrook, IL 60062

Marketed by:
Astellas Pharma US, Inc., Northbrook, IL 60062
Medivation, Inc., San Francisco, CA 94105

15C018-XTA

Rx Only

XTANDI® is a registered trademark of Astellas Pharma Inc.

PATIENT INFORMATION
XTANDI® (ex TAN dee)
(enzalutamide)
capsules

What is XTANDI?

XTANDI is a prescription medicine used to treat men with prostate cancer that no longer responds to a medical or surgical treatment that lowers testosterone and that has spread to other parts of the body.

It is not known if XTANDI is safe and effective in children.

Who should not take XTANDI?

XTANDI is not for use in women.

Do not take XTANDI if you are pregnant or may become pregnant. XTANDI can harm your unborn baby.

What should I tell my healthcare provider before taking XTANDI?

Before you take XTANDI, tell your healthcare provider if you:

- have a history of seizures, brain injury, stroke, or brain tumors
- have any other medical conditions
- have a partner who is pregnant or may become pregnant. Men who are sexually active with a pregnant woman must use a condom during and for 3 months after treatment with XTANDI. If your sexual partner may become pregnant, a condom and another form of effective birth control must be used during and for 3 months after treatment. Talk with your healthcare provider if you have questions about birth control. See **"Who should not take XTANDI?"**

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. XTANDI may affect the way other medicines work, and other medicines may affect how XTANDI works.

You should not start or stop any medicine before you talk with the healthcare provider that prescribed XTANDI.

Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist when you get a new medicine.

How should I take XTANDI?

- Take XTANDI exactly as your healthcare provider tells you.
- Take your prescribed dose of XTANDI one time a day, at the same time each day.
- Your healthcare provider may change your dose if needed.
- Do not change or stop taking your prescribed dose of XTANDI without talking with your healthcare provider first.
- XTANDI can be taken with or without food.
- Swallow XTANDI capsules whole. Do not chew, dissolve, or open the capsules.
- If you miss a dose of XTANDI, take your prescribed dose as soon as you remember that day. If you miss your daily dose, take your prescribed dose at your regular time the next day. Do not take more than your prescribed dose of XTANDI in one day.

If you take too much XTANDI, call your healthcare provider or go to the nearest emergency room right away. You may have an increased risk of seizure if you take too much XTANDI.

What are the possible side effects of XTANDI?

XTANDI may cause serious side effects including:

- **Seizure.** If you take XTANDI you may be at risk of having a seizure. You should avoid activities where a sudden loss of consciousness could cause serious harm to yourself or others. Tell your healthcare provider right away if you have loss of consciousness or seizure. Your healthcare provider will stop XTANDI if you have a seizure during treatment.

- **Posterior Reversible Encephalopathy Syndrome (PRES).** If you take XTANDI you may be at risk of developing a condition involving the brain called PRES. Tell your healthcare provider right away if you have a seizure or quickly worsening symptoms such as headache, decreased alertness, confusion, reduced eyesight, blurred vision or other visual problems. Your healthcare provider will do a test to check for PRES. Your healthcare provider will stop XTANDI if you develop PRES.

The most common side effects of XTANDI include:

- weakness or feeling more tired than usual
- back pain
- decreased appetite
- constipation
- joint pain
- diarrhea
- hot flashes
- upper respiratory tract infection
- swelling in your hands, arms, legs, or feet
- shortness of breath
- muscle and bone pain
- weight loss
- headache
- high blood pressure
- dizziness
- a feeling that you or things around you are moving or spinning (vertigo)

XTANDI may cause infections, falls and injuries from falls. Tell your healthcare provider if you have signs or symptoms of an infection or if you fall.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of XTANDI. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XTANDI?

- Store XTANDI between 68°F to 77°F (20°C to 25°C).
- Keep XTANDI capsules dry and in a tightly closed container.

Keep XTANDI and all medicines out of the reach of children.

General information about XTANDI.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use XTANDI for a condition for which it was not prescribed. Do not give XTANDI to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about XTANDI. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about XTANDI that is written for health professionals.

For more information go to www.Xtandi.com or call 1-800-727-7003.

What are the ingredients in XTANDI?

Active ingredient: enzalutamide

Inactive ingredients: caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, black iron oxide

Manufactured by: Catalent Pharma Solutions, LLC, St. Petersburg, FL 33716

Marketed by: Astellas Pharma US, Inc., Northbrook, IL 60062 Medivation Inc., San Francisco, CA 94105

15C018-XTA

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: October 2015

Appendix 5: ZYTIGA® Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZYTIGA safely and effectively. See full prescribing information for ZYTIGA.

ZYTIGA™ (abiraterone acetate) Tablets
For Oral Administration
Initial U.S. Approval – 2011

----------INDICATIONS AND USAGE----------
ZYTIGA is a CYP17 inhibitor indicated for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel. (1)

----------DOSAGE AND ADMINISTRATION----------
Recommended dose: ZYTIGA 1,000 mg administered orally once daily in combination with prednisone 5 mg administered orally twice daily. ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. (2.1)

- For patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the ZYTIGA starting dose to 250 mg once daily. (2.2)
- For patients who develop hepatotoxicity during treatment, hold ZYTIGA until recovery. Retreatment may be initiated at a reduced dose. ZYTIGA should be discontinued if patients develop severe hepatotoxicity. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Tablet 250 mg (3)

----------CONTRAINDICATIONS----------
- ZYTIGA is contraindicated in women who are or may become pregnant. (4.1)

----------WARNINGS AND PRECAUTIONS----------
- Mineralocorticoid excess: Use ZYTIGA with caution in patients with a history of cardiovascular disease. The safety of ZYTIGA in patients with LVEF < 50% or NYHA Class III or IV heart failure is not established. Control hypertension and correct hypokalemia before treatment. Monitor blood pressure, serum potassium and symptoms of fluid retention at least monthly. (5.1)
- Adrenocortical insufficiency: Monitor for symptoms and signs of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations. (5.2)
- Hepatotoxicity: Increases in liver enzymes have lead to drug interruption, dose modification and/or discontinuation. Monitor liver function and modify, interrupt, or discontinue ZYTIGA dosing as recommended. (5.3)
- Food Effect: ZYTIGA must be taken on an empty stomach. Exposure (area under the curve) of abiraterone increases up to 10 fold when abiraterone acetate is taken with meals. (5.4)

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥ 5%) are joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, and upper respiratory tract infection. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Centocor Ortho Biotech Inc. at 800-457-6399 and *www.centocorortho biotech.com* or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Avoid co-administration of ZYTIGA with CYP2D6 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate. (7)

----------USE IN SPECIFIC POPULATIONS----------
- Do not use ZYTIGA in patients with baseline severe hepatic impairment (Child-Pugh Class C). (8.6)

See 17 for Patient Counseling Information and FDA-approved patient labeling.

Issued: [April 2011]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZYTIGA in combination with prednisone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) who have received prior chemotherapy containing docetaxel.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of ZYTIGA is 1,000 mg administered orally once daily in combination with prednisone 5 mg administered orally twice daily. ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken *[see Clinical Pharmacology (12.3)]*. The tablets should be swallowed whole with water.

2.2 Dose Modification Guidelines

Hepatic Impairment

In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. A once daily dose of 250 mg in patients with moderate hepatic impairment is predicted to result in an area under the concentration curve (AUC) similar to the AUC seen in patients with normal hepatic function receiving 1,000 mg once daily. However, there are no clinical data at the dose of 250 mg once daily in patients with moderate hepatic impairment and caution is advised. In patients with moderate hepatic impairment monitor ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. If elevations in ALT and/or AST greater than 5X upper limit of normal (ULN) or total bilirubin greater than 3X ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA and do not re-treat patients with ZYTIGA *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

Avoid ZYTIGA in patients with baseline severe hepatic impairment (Child-Pugh Class C), as ZYTIGA has not been studied in this population, and no dose adjustment can be predicted.

Hepatotoxicity

For patients who develop hepatotoxicity during treatment with ZYTIGA (ALT and/or AST greater than 5X ULN or total bilirubin greater than 3X ULN), interrupt treatment with ZYTIGA *[see Warnings and Precautions (5.3)]*. Treatment may be restarted at a reduced dose of 750 mg once daily following return of liver function tests to the patient's baseline or

to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN. For patients who resume treatment, monitor serum transaminases and bilirubin at a minimum of every two weeks for three months and monthly thereafter.

If hepatotoxicity recurs at the dose of 750 mg once daily, re-treatment may be restarted at a reduced dose of 500 mg once daily following return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN.

If hepatotoxicity recurs at the reduced dose of 500 mg once daily, discontinue treatment with ZYTIGA. The safety of ZYTIGA re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

3 DOSAGE FORMS AND STRENGTHS

ZYTIGA (abiraterone acetate) 250 mg tablets are white to off-white, oval-shaped tablets debossed with AA250 on one side.

4 CONTRAINDICATIONS

4.1 Pregnancy

ZYTIGA may cause fetal harm when administered to a pregnant woman. ZYTIGA is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

5 WARNINGS AND PRECAUTIONS

5.1 Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess

Use ZYTIGA with caution in patients with a history of cardiovascular disease. ZYTIGA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition *[see Adverse Reactions (6) and Clinical Pharmacology (12.1)]*. Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. The safety of ZYTIGA in patients with left ventricular ejection fraction <50% or NYHA Class III or IV heart failure has not been established because these patients were excluded from the randomized clinical trial. Monitor patients for hypertension, hypokalemia,

and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with ZYTIGA.

5.2 Adrenocortical Insufficiency

Adrenocortical insufficiency has been reported in clinical trials in patients receiving ZYTIGA in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations *[see Warnings and Precautions (5.1)]*.

5.3 Hepatotoxicity

Marked increases in liver enzymes leading to drug discontinuation or dosage modification have occurred *[see Adverse Reactions (6)]*. Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA, every two weeks for the first three months of treatment and monthly thereafter. In patients with baseline moderate hepatic impairment receiving a reduced ZYTIGA dose of 250 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt ZYTIGA treatment and closely monitor liver function.

Re-treatment with ZYTIGA at a reduced dose level may take place only after return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN *[see Dosage and Administration (2.2)]*.

The safety of ZYTIGA re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

5.4 Food effect

ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of

ZYTIGA is taken. Abiraterone C_{max} and $AUC_{0-\infty}$ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state. The safety of these increased exposures when multiple doses of abiraterone acetate are taken with food has not been assessed *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Hypertension, hypokalemia, and fluid retention due to mineralocorticoid excess *[see Warnings and Precautions (5.1)]*.
- Adrenocortical insufficiency *[see Warnings and Precautions (5.2)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*.
- Food effect *[see Warnings and Precautions (5.4)]*.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In a placebo-controlled, multicenter phase 3 clinical trial of patients with metastatic castration-resistant prostate cancer who were using a gonadotropin-releasing hormone (GnRH) agonist or were previously treated with orchiectomy, ZYTIGA was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arm (N = 791). Placebo plus prednisone 5 mg twice daily was given to control patients (N = 394). The median duration of treatment with ZYTIGA was 8 months.

The most common adverse drug reactions (≥5%) reported in clinical studies were joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, and upper respiratory tract infection.

The most common adverse drug reactions that resulted in drug discontinuation were aspartate aminotransferase increased, alanine aminotransferase increased, urosepsis and cardiac failure (each in <1% of patients taking ZYTIGA).

Adverse reactions and laboratory abnormalities related to mineralocorticoid effects were reported more commonly in patients treated with ZYTIGA than in patients treated with placebo: hypokalemia 28% versus 20%, hypertension 9% versus 7% and fluid retention (edema) 27% versus 18%, respectively (see Table 1). In patients treated with ZYTIGA,

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grades 3 to 4 hypokalemia occurred in 5% of patients and grades 3 to 4 hypertension was reported in 1% of patients *[see Warnings and Precautions (5.1)]*.

Table 1 shows adverse reactions due to ZYTIGA that occurred with either a ≥ 2% absolute increase in frequency compared to placebo, or were events of special interest (mineralocorticoid excess, cardiac adverse reactions, and liver toxicities).

Table 1: Adverse Reactions due to ZYTIGA in a Placebo-Controlled Phase 3 Trial

	ZYTIGA with Prednisone (N=791)		Placebo with Prednisone (N=394)	
System/Organ Class Adverse reaction	All Grades[1] %	Grade 3-4 %	All Grades %	Grade 3-4 %
Musculoskeletal and connective tissue disorders				
Joint swelling/ discomfort[2]	29.5	4.2	23.4	4.1
Muscle discomfort[3]	26.2	3.0	23.1	2.3
General disorders				
Edema[4]	26.7	1.9	18.3	0.8
Vascular disorders				
Hot flush	19.0	0.3	16.8	0.3
Hypertension	8.5	1.3	6.9	0.3
Gastrointestinal disorders				
Diarrhea	17.6	0.6	13.5	1.3
Dyspepsia	6.1	0	3.3	0
Infections and infestations				
Urinary tract infection	11.5	2.1	7.1	0.5
Upper respiratory tract infection	5.4	0	2.5	0
Respiratory, thoracic and mediastinal disorders				
Cough	10.6	0	7.6	0
Renal and urinary disorders				
Urinary frequency	7.2	0.3	5.1	0.3
Nocturia	6.2	0	4.1	0
Cardiac disorders				
Arrhythmia[5]	7.2	1.1	4.6	1.0
Chest pain or chest discomfort[6]	3.8	0.5	2.8	0
Cardiac failure[7]	2.3	1.9	1.0	0.3

[1] Adverse events graded according to CTCAE version 3.0
[2] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness,
[3] Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness
[4] Includes terms Edema, Edema peripheral, Pitting edema, and Generalised edema
[5] Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia.
[6] Includes terms Angina pectoris, Chest pain, and Angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the ZYTIGA arm (1.3% vs. 1.1% respectively).
[7] Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

Cardiovascular Adverse Reactions:

Cardiovascular adverse reactions in the phase 3 trial are shown in Table 1. The majority of arrhythmias were grade 1 or 2. Grade 3-4 arrhythmias occurred at similar rates in the two arms. There was one death associated with arrhythmia and one patient with sudden death in the ZYTIGA arm. No patients had sudden death or arrhythmia associated with death in the placebo arm. Cardiac ischemia or myocardial infarction led to death in 2 patients in the placebo arm and 1 death in the ZYTIGA arm. Cardiac failure resulting in death occurred in 1 patient on both arms.

Hepatotoxicity:
Drug-associated hepatotoxicity with elevated ALT, AST, and total bilirubin has been reported in patients treated with ZYTIGA. Across all clinical trials, liver function test elevations (ALT or AST increases of > 5X ULN) were reported in 2.3% of patients who received ZYTIGA, typically during the first 3 months after starting treatment. In the phase 3 trial, patients whose baseline ALT or AST were elevated were more likely to experience liver function test elevations than those beginning with normal values. When elevations of either ALT or AST > 5X ULN, or elevations in bilirubin > 3X ULN were observed, ZYTIGA was withheld or discontinued. In two instances marked increases in liver function tests occurred *[see Warnings and Precautions (5.2)]*. These two patients with normal baseline hepatic function, experienced ALT or AST elevations 15 to 40X ULN and bilirubin elevations 2 to 6 X ULN. Upon discontinuation of ZYTIGA, both patients had normalization of their liver function tests and one patient was re-treated with ZYTIGA without recurrence of the elevations.

In clinical trials, the following patients were excluded: patients with active hepatitis, patients with baseline ALT and/or AST ≥ 2.5X ULN in the absence of liver metastases, and patients with ALT and/or AST > 5X ULN in the presence of liver metastases. Abnormal liver function tests developing in patients participating in clinical trials were managed by treatment interruption, dose modification and/or discontinuation *[see Dosage and Administration (2.2) and Warnings and Precautions (5.3)]*. Patients with elevations of ALT or AST > 20X ULN were not re-treated.

Other Adverse Reactions:
Adrenal insufficiency occurred in two patients on the abiraterone arm of the phase 3 clinical trial (< 1%).

Laboratory Abnormalities of Interest:

Table 2 shows laboratory values of interest from the phase 3 placebo-controlled clinical trial. Grade 3-4 low serum phosphate (7.2%) and potassium (5.3%) occurred more frequently in the ZYTIGA arm.

Table 2: Laboratory Abnormalities of Interest in a Phase 3 Placebo-Controlled Clinical Trial

Laboratory Abnormality	Abiraterone (N=791)		Placebo (N=394)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
High Triglyceride	62.5	0.4	53.0	0
High AST	30.6	2.1	36.3	1.5
Low Potassium	28.3	5.3	19.8	1.0
Low Phosphorus	23.8	7.2	15.7	5.8
High ALT	11.1	1.4	10.4	0.8
High total Bilirubin	6.6	0.1	4.6	0

7 DRUG INTERACTIONS

7.1 Effects of Abiraterone on Drug Metabolizing Enzymes

ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug *[see Clinical Pharmacology (12.3)]*.

7.2 Drugs that Inhibit or Induce CYP3A4 Enzymes

Based on *in vitro* data, ZYTIGA is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated, *in vivo*. Avoid or use with caution, strong inhibitors and inducers of CYP3A4 during ZYTIGA treatment *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X *[see Contraindications (4.1)]*.

ZYTIGA is contraindicated in women who are or may become pregnant while receiving the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and the potential risk for pregnancy loss. Women of childbearing potential should be advised to avoid becoming pregnant during treatment with ZYTIGA.

8.3 Nursing Mothers

ZYTIGA is not indicated for use in women. It is not known if abiraterone acetate is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ZYTIGA, a decision should be made to either discontinue nursing, or discontinue the drug taking into account the importance of the drug to the mother.

8.4 Pediatric Use

ZYTIGA is not indicated in children.

8.5 Geriatric Use

Of the total number of patients in a phase 3 trial of ZYTIGA, 71% of patients were 65 years and over and 28% were 75 years and over. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients.

8.6 Patients with Hepatic Impairment

The pharmacokinetics of abiraterone were examined in subjects with baseline mild (n = 8) or moderate (n = 8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone after a single oral 1,000 mg dose of ZYTIGA increased by approximately 1.1-fold and 3.6 fold in subjects with mild and moderate baseline hepatic impairment, respectively compared to subjects with normal hepatic function.

No dosage adjustment is necessary for patients with baseline mild hepatic impairment. In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. If elevations in ALT or AST >5X ULN or total bilirubin >3X ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA treatment *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)]*.

The safety of ZYTIGA in patients with baseline severe hepatic impairment has not been studied. These patients should not receive ZYTIGA.

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For patients who develop hepatotoxicity during treatment, interruption of treatment and dosage adjustment may be required *[see Dosage and Administration (2.2), Warnings and Precautions (5.2), and Clinical Pharmacology (12.3)]*.

8.7 Patients with Renal Impairment

In a dedicated renal impairment trial, the mean PK parameters were comparable between healthy subjects with normal renal function (N=8) and those with end stage renal disease (ESRD) on hemodialysis (N=8) after a single oral 1,000 mg dose of ZYTIGA. No dosage adjustment is necessary for patients with renal impairment *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

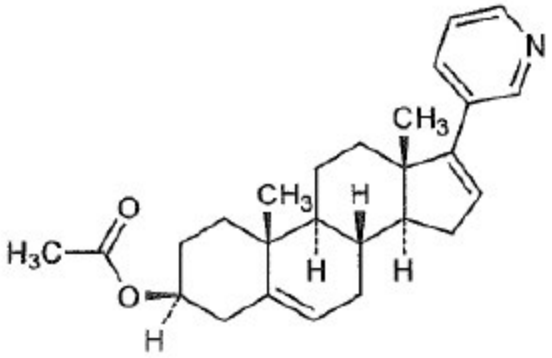
10 OVERDOSAGE

There have been no reports of overdose of ZYTIGA during clinical studies.

There is no specific antidote. In the event of an overdose, stop ZYTIGA, undertake general supportive measures, including monitoring for arrhythmias and cardiac failure and assess liver function.

11 DESCRIPTION

Abiraterone acetate, the active ingredient of ZYTIGA is the acetyl ester of abiraterone. Abiraterone is an inhibitor of CYP17 (17α-hydroxylase/C17,20-lyase). Each ZYTIGA tablet contains 250 mg of abiraterone acetate. Abiraterone acetate is designated chemically as (3β)-17-(3-pyridinyl)androsta-5,16-dien-3-yl acetate and its structure is:



Abiraterone acetate is a white to off-white, non-hygroscopic, crystalline powder. Its molecular formula is $C_{26}H_{33}NO_2$ and it has a molecular weight of 391.55. Abiraterone acetate is a lipophilic compound with an octanol-water partition coefficient of 5.12 (Log P) and is practically insoluble in water. The pKa of the aromatic nitrogen is 5.19.

Inactive ingredients in the tablets are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate, and colloidal silicon dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Abiraterone acetate (ZYTIGA) is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17 α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis.

CYP17 catalyzes two sequential reactions: 1) the conversion of pregnenolone and progesterone to their 17α-hydroxy derivatives by 17α-hydroxylase activity and 2) the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively, by C17, 20 lyase activity. DHEA and androstenedione are androgens and are precursors of testosterone. Inhibition of CYP17 by abiraterone can also result in increased mineralocorticoid production by the adrenals *(see Warnings and Precautions [5.1])*.

Androgen sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with GnRH agonists or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumor.

ZYTIGA decreased serum testosterone and other androgens in patients in the placebo-controlled phase 3 clinical trial. It is not necessary to monitor the effect of ZYTIGA on serum testosterone levels.

Changes in serum prostate specific antigen (PSA) levels may be observed but have not been shown to correlate with clinical benefit in individual patients.

12.3 Pharmacokinetics

Following administration of abiraterone acetate, the pharmacokinetics of abiraterone and abiraterone acetate have been studied in healthy subjects and in patients with metastatic castration-resistant prostate cancer (CRPC). *In vivo*, abiraterone acetate is converted to abiraterone. In clinical studies, abiraterone acetate plasma concentrations were below detectable levels (< 0.2 ng/mL) in > 99% of the analyzed samples.

Absorption

Following oral administration of abiraterone acetate to patients with metastatic CRPC, the median time to reach maximum plasma abiraterone concentrations is 2 hours. Abiraterone

accumulation is observed at steady-state, with a 2-fold higher exposure (steady-state AUC) compared to a single 1,000 mg dose of abiraterone acetate.

At the dose of 1,000 mg daily in patients with metastatic CRPC, steady-state values (mean ± SD) of C_{max} were 226 ± 178 ng/mL and of AUC were 1173 ± 690 ng.hr/mL. No major deviation from dose proportionality was observed in the dose range of 250 mg to 1,000 mg.

Systemic exposure of abiraterone is increased when abiraterone acetate is administered with food. Abiraterone C_{max} and $AUC_{0-\infty}$ were approximately 7- and 5-fold higher, respectively, when abiraterone acetate was administered with a low-fat meal (7% fat, 300 calories) and approximately 17- and 10-fold higher, respectively, when abiraterone acetate was administered with a high-fat (57% fat, 825 calories) meal. Given the normal variation in the content and composition of meals, taking ZYTIGA with meals has the potential to result in increased and highly variable exposures. Therefore, no food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. The tablets should be swallowed whole with water *[see Dosage and Administration (2.1)]*.

Distribution and Protein Binding

Abiraterone is highly bound (>99%) to the human plasma proteins, albumin and alpha-1 acid glycoprotein. The apparent steady-state volume of distribution (mean ± SD) is 19,669 ± 13,358 L. *In vitro* studies show that at clinically relevant concentrations, abiraterone acetate and abiraterone are not substrates of P-glycoprotein (P-gp) and that abiraterone acetate is an inhibitor of P-gp. No studies have been conducted with other transporter proteins.

Metabolism

Following oral administration of ^{14}C-abiraterone acetate as capsules, abiraterone acetate is hydrolyzed to abiraterone (active metabolite). The conversion is likely through esterase activity (the esterases have not been identified) and is not CYP mediated. The two main circulating metabolites of abiraterone in human plasma are abiraterone sulphate (inactive) and N-oxide abiraterone sulphate (inactive), which account for about 43% of exposure each. CYP3A4 and SULT2A1 are the enzymes involved in the formation of N-oxide abiraterone sulphate and SULT2A1 is involved in the formation of abiraterone sulphate.

Excretion

In patients with metastatic CRPC, the mean terminal half-life of abiraterone in plasma (mean ± SD) is 12 ± 5 hours. Following oral administration of ^{14}C-abiraterone acetate, approximately 88% of the radioactive dose is recovered in feces and approximately 5% in

urine. The major compounds present in feces are unchanged abiraterone acetate and abiraterone (approximately 55% and 22% of the administered dose, respectively).

Patients with Hepatic Impairment

The pharmacokinetics of abiraterone was examined in subjects with baseline mild (n = 8) or moderate (n = 8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. Systemic exposure to abiraterone after a single oral 1,000 mg dose given under fasting conditions increased approximately 1.1-fold and 3.6-fold in subjects with mild and moderate baseline hepatic impairment, respectively. The mean half-life of abiraterone is prolonged to approximately 18 hours in subjects with mild hepatic impairment and to approximately 19 hours in subjects with moderate hepatic impairment. ZYTIGA has not been studied in patients with baseline severe hepatic impairment (Child-Pugh Class C) *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*.

Patients with Renal Impairment

The pharmacokinetics of abiraterone were examined in patients with end-stage renal disease (ESRD) on a stable hemodialysis schedule (N=8) and in matched control subjects with normal renal function (N=8). In the ESRD cohort of the trial, a single 1,000 mg ZYTIGA dose was given under fasting conditions 1 hour after dialysis, and samples for pharmacokinetic analysis were collected up to 96 hours post dose. Systemic exposure to abiraterone after a single oral 1,000 mg dose did not increase in subjects with end-stage renal disease on dialysis, compared to subjects with normal renal function *[see Use in Specific Populations (8.7)]*.

Drug Interactions

In vitro studies with human hepatic microsomes showed that abiraterone is a strong inhibitor of CYP1A2 and CYP2D6 and a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5.

In an *in vivo* drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively when dextromethorphan 30 mg was given with abiraterone acetate 1,000 mg daily (plus prednisone 5 mg twice daily). The AUC for dextrorphan, the active metabolite of dextromethorphan, increased approximately 1.3 fold *[see Drug Interactions (7.1)]*.

In a clinical study to determine the effects of abiraterone acetate 1,000 mg daily (plus prednisone 5 mg twice daily) on a single 100 mg dose of the CYP1A2 substrate theophylline, no increase in systemic exposure of theophylline was observed.

Abiraterone is a substrate of CYP3A4, *in vitro*. The effects of strong CYP3A4 inhibitors or inducers on the pharmacokinetics of abiraterone have not been evaluated, *in vivo*. Strong inhibitors and inducers of CYP3A4 should be avoided or used with caution *[see Drug Interactions (7.2)]*.

12.4 QT Prolongation

In a multi-center, open-label, single-arm trial, 33 patients with metastatic CRPC received ZYTIGA orally at a dose of 1,000 mg once daily at least 1 hour before or 2 hours after a meal in combination with prednisone 5 mg orally twice daily. Assessments up to Cycle 2 Day 2 showed no large changes in the QTc interval (i.e., >20 ms) from baseline. However, small increases in the QTc interval (i.e., <10 ms) due to abiraterone acetate cannot be excluded due to study design limitations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

Abiraterone acetate and abiraterone did not induce mutations in the microbial mutagenesis (Ames) assay and was not clastogenic in both the *in vitro* cytogenetic assay using primary human lymphocytes and in the *in vivo* rat micronucleus assay.

Developmental or reproductive toxicology studies were not conducted with abiraterone acetate. In studies in rats (13- and 26-weeks) and monkeys (39-weeks), atrophy, aspermia/hypospermia, and hyperplasia in the reproductive system were observed at ≥50 mg/kg/day in rats and ≥250 mg/kg/day in monkeys and were consistent with the antiandrogenic pharmacological activity of abiraterone *[see Nonclinical Toxicology (13.2.)]*. These effects were observed in rats and monkeys at approximately 1.14 and 0.6 the human clinical exposure based on AUC, respectively.

13.2 Animal Toxicology and/or Pharmacology

In 13- and 26-week studies in rats and 13- and 39-week studies in monkeys, a reduction in circulating testosterone levels occurred with abiraterone acetate at approximately one half the human clinical exposure based on AUC. As a result, decreases in organ weights and toxicities were observed in the male and female reproductive system, adrenal glands, liver, pituitary (rats only), and male mammary glands. The changes in the reproductive organs are consistent with the antiandrogenic pharmacological activity of abiraterone acetate. A dose-dependent increase in cataracts was observed in rats at 26 weeks starting at ≥50 mg/kg/day (1.14X the human clinical exposure based on AUC). In the 39-week monkey study, no

cataracts were observed at higher doses (2X the clinical exposure based on AUC). All other toxicities associated with abiraterone acetate reversed or were partially resolved after a 4-week recovery period.

14 CLINICAL STUDIES

The efficacy and safety of ZYTIGA in patients with metastatic castration-resistant prostate cancer (CRPC) who had received prior chemotherapy containing docetaxel were assessed in a randomized, placebo-controlled, multicenter phase 3 clinical trial. A total of 1195 patients were randomized 2:1 to receive either ZYTIGA orally at a dose of 1,000 mg once daily in combination with prednisone 5 mg orally twice daily (N=797) or placebo once daily plus prednisone 5 mg orally twice daily (N=398). Patients randomized to either arm were to continue treatment until disease progression (defined as a 25% increase in PSA over the patient's baseline/nadir together with protocol-defined radiographic progression and symptomatic or clinical progression), initiation of new treatment, unacceptable toxicity or withdrawal. Patients with prior ketoconazole treatment for prostate cancer and a history of adrenal gland or pituitary disorders were excluded from this trial.

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 69 years (range 39-95) and the racial distribution was 93.3% Caucasian, 3.6% Black, 1.7% Asian, and 1.6% Other. Eighty-nine percent of patients enrolled had an ECOG performance status score of 0-1 and 45% had a Brief Pain Inventory score of $\geq$ 4 (patient's reported worst pain over the previous 24 hours). Ninety percent of patients had metastases in bone and 30% had visceral involvement. Seventy percent of patients had radiographic evidence of disease progression and 30% had PSA-only progression. Seventy percent of patients had previously received one cytotoxic chemotherapy regimen and 30% received two regimens.

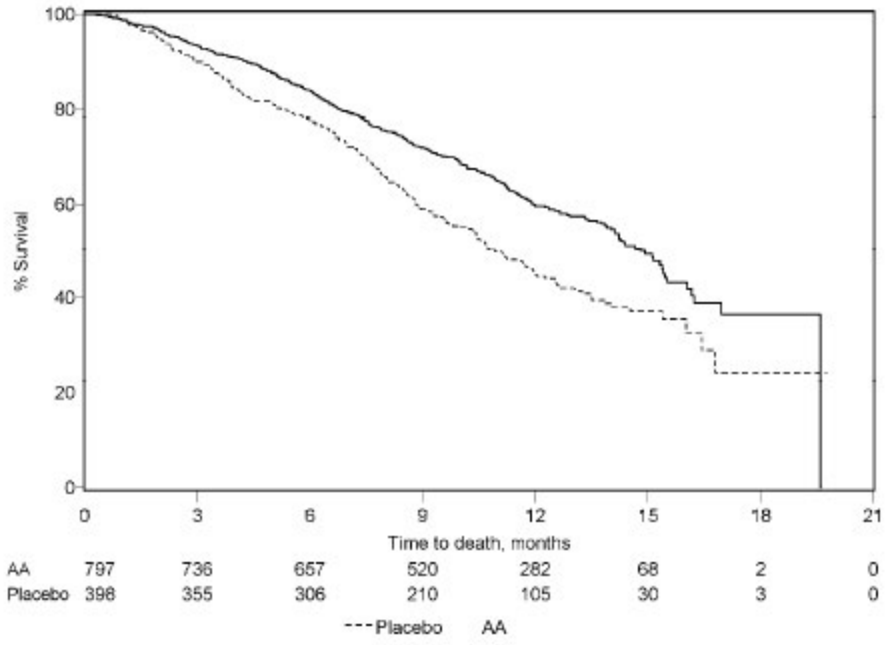
The protocol pre-specified interim analysis was conducted after 552 deaths and showed a statistically significant improvement in overall survival in patients treated with ZYTIGA compared to patients in the placebo arm (Table 3 and Figure 1). An updated survival analysis was conducted when 775 deaths (97% of the planned number of deaths for final analysis) were observed. Results from this analysis were consistent with those from the interim analysis (Table 3).

Table 3: Overall Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone (Intent-to-Treat Analysis)

	ZYTIGA (N=797)	Placebo (N=398)
Primary Survival Analysis		
Deaths (%)	333 (42%)	219 (55%)
Median survival (months) (95% CI)	14.8 (14.1, 15.4)	10.9 (10.2, 12.0)
p value [a]	< 0.0001	
Hazard ratio (95% CI) [b]	0.646 (0.543, 0.768)	
Updated Survival Analysis		
Deaths (%)	501 (63%)	274 (69%)
Median survival (months) (95% CI)	15.8 (14.8, 17.0)	11.2 (10.4, 13.1)
Hazard ratio (95% CI) [b]	0.740 (0.638, 0.859)	

[a]P-value is derived from a log-rank test stratified by ECOG performance status score (0-1 vs. 2), pain score (absent vs. present), number of prior chemotherapy regimens (1 vs. 2), and type of disease progression (PSA only vs. radiographic).
[b]Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors ZYTIGA

Figure 1: Kaplan-Meier Overall Survival Curves (Intent-to-Treat Analysis)



AA= ZYTIGA

16 HOW SUPPLIED/STORAGE AND HANDLING

ZYTIGA (abiraterone acetate) 250 mg tablets are white to off-white, oval tablets debossed with AA250 on one side. ZYTIGA 250 mg tablets are available in high-density polyethylene bottles of 120 tablets.

NDC Number 57894-150-12

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) *[see USP controlled room temperature]*.

Based on its mechanism of action, ZYTIGA may harm a developing fetus. Therefore, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves *[see Use in Specific Populations (8.1)]*.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

- Patients should be informed that ZYTIGA and prednisone are used together and that they should not interrupt or stop either of these medications without consulting their physician.
- Patients receiving GnRH agonists should be informed that they need to maintain this treatment during the course of treatment with ZYTIGA and prednisone.
- Patients should be informed that ZYTIGA must not be taken with food and that no food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. They should be informed that the tablets should be swallowed whole with water. Patients should be informed that taking ZYTIGA with food causes increased exposure and this may result in adverse reactions.
- Patients should be informed that ZYTIGA is taken once daily and prednisone is taken twice daily according to their physician's instructions.
- Patients should be informed that in the event of a missed daily dose of ZYTIGA or prednisone, they should take their normal dose the following day. If more than one daily dose is skipped, patients should be told to inform their physician.
- Patients should be apprised of the common side effects associated with ZYTIGA, including peripheral edema, hypokalemia, hypertension and urinary tract infection. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Patients should be advised that their liver function will be monitored using blood tests.
- Patients should be informed that ZYTIGA may harm a developing fetus; thus, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves. Patients should also be informed that it is not known whether

abiraterone or its metabolites are present in semen and they should use a condom if having sex with a pregnant woman. The patient should use a condom and another effective method of birth control if he is having sex with a woman of child-bearing potential. These measures are required during and for one week after treatment with ZYTIGA.

Manufactured by:

Patheon Inc.

Toronto, Canada

Manufactured for:

Centocor Ortho Biotech Inc.

Horsham, PA 19044

Revised: April 2011

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PATIENT INFORMATION
ZYTIGA™ (Zye-**tee**-ga)
(abiraterone acetate)
Tablets

Read this Patient information that comes with ZYTIGA before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is ZYTIGA?

ZYTIGA is a prescription medicine that is used along with prednisone. ZYTIGA is used to treat men with castration-resistant prostate cancer (prostate cancer that is resistant to medical or surgical treatments that lower testosterone) that has spread to other parts of the body and who have received treatment with docetaxel.

ZYTIGA is not for use in women or children.

Who should not take ZYTIGA?

Do not take ZYTIGA if you are pregnant or may become pregnant. ZYTIGA may harm your unborn baby.

Women who are pregnant or who may become pregnant should not touch ZYTIGA without protection, such as gloves.

What should I tell my healthcare provider before taking ZYTIGA?

Before you take ZYTIGA, tell your healthcare provider if you:

- have heart problems
- have liver problems
- have a history of adrenal and or pituitary problems
- have any other medical conditions
- plan to become pregnant. See "Who should not take ZYTIGA?"
- are breastfeeding or plan to breastfeed. It is not known if ZYTIGA passes into your breast milk. You and your healthcare provider should decide if you will take ZYTIGA or breastfeed. You should not do both. See "Who should not take ZYTIGA?"

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. ZYTIGA can interact with many other medicines.

You should not start or stop any medicine before you talk with the healthcare provider that prescribed ZYTIGA.

Know the medicines you take. Keep a list of them with you to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take ZYTIGA?

- Take ZYTIGA and prednisone exactly as your healthcare provider tells you.
- Your healthcare provider may change your dose if needed.
- Do not stop taking your prescribed dose of ZYTIGA or prednisone without talking with your healthcare provider first.
- Take ZYTIGA on an empty stomach. **Do not take ZYTIGA with food.** Taking ZYTIGA with food may cause more of the medicine to be absorbed by the body than is needed and this may cause side effects.
- No food should be eaten 2 hours before and 1 hour after taking ZYTIGA.
- Swallow ZYTIGA tablets whole.
- Take ZYTIGA tablets with water.
- Men who are sexually active with a pregnant women must use a condom during and for one week after treatment with ZYTIGA. If their sexual partner may become pregnant, a condom and another form of birth control must be used during and for one week after treatment with ZYTIGA. Talk with your healthcare provider if you have questions about birth control.
- If you miss a dose of ZYTIGA or prednisone, take your prescribed dose the following day. If you miss more than 1 dose, tell your healthcare provider right away.
- Your healthcare provider will do blood tests to check for side effects.

What are the possible side effects of ZYTIGA?

ZYTIGA may cause serious side effects including:

- **High blood pressure (hypertension), low blood potassium levels (hypokalemia) and fluid retention (edema).** Tell your healthcare provider if you get any of the following symptoms:
  - dizziness
  - fast heartbeats
  - feel faint or lightheaded
  - headache
  - confusion
  - muscle weakness
  - pain in your legs
  - swelling in your legs or feet

- **Adrenal problems** may happen if you stop taking prednisone, get an infection, or are under stress.

- **Liver problems.** Your healthcare provider will do blood test to check your liver before treatment with ZYTIGA and during treatment with ZYTIGA.

The most common side effects of ZYTIGA include:

- joint swelling or pain
- muscle aches
- hot flushes
- diarhea
- urinary tract infection
- cough
- irregular heartbeats
- urinate more often than normal
- need to get up at night to urinate
- heartburn
- cold like symptoms

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ZYTIGA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZYTIGA?

- Store ZYTIGA at 59°F to 86°F (15°C to 30°C).

Keep ZYTIGA and all medicines out of the reach of children.

General information about ZYTIGA.

Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. Do not use ZYTIGA for a condition for which it was not prescribed. Do not give your ZYTIGA to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about ZYTIGA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ZYTIGA that is written for healthcare professionals.

For more information contact Centocor Ortho Biotech, Inc. at 1-800-457-6399 or *www.Zytiga.com*.

What are the ingredients of ZYTIGA?

Active ingredient: abiraterone acetate

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate and colloidal silicon dioxide.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Patheon Inc.
Toronto, Canada
Manufactured for:
Centocor Ortho Biotech Inc.
Horsham, PA 19044

Issued: April 2011

Reference ID: 2939553

Appendix 6: Investigator Agreement Page

Phase 1b Safety and Tolerability Study of ZEN003694 in Combination with Enzalutamide or Abiraterone in Patients with Metastatic Castration-resistant Prostate Cancer

Protocol ZEN003694-002
Amendment 10: 05 November 2018

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. Further, I agree to conduct this study in accordance with ICH Guidelines, all applicable United States (US) Regulations (21 CFR parts 50, 54, 56 and 312) and Good Clinical Practice and applicable regulatory requirements.

The information contained in this protocol is proprietary and provided to me in confidence, and may not be disclosed to any other party, in any form, without prior authorization from Zenith Epigenetics Ltd., except to the extent necessary for the conduct of the study at this study site.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Zenith Epigenetics Ltd. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator's Signature **Date**

Principal Investigator's Name: (Print)

Institution's Name, City, State: