TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Phase I, Open-Label, Dose-Finding Study of GSK2636771 Administered in Combination with Enzalutamide (Xtandi) in Male Subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Compound Number: GSK2636771

Development Phase: I

Effective Date: 27-JAN-2017

Protocol Amendment Number: 04

Author (s): PPD
PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2013N172718_00	2014-MAY-22	Original
2013N172718_01	2014-SEP-08	Amendment No. 1
Amendment 1 incorporates changes to Section 5.2, Permanent Discontinuation of Study Treatment(s) for clarification as requested by the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom		
2013N172718_02	2015-FEB-26	Amendment No. 2
Amendment 2 was completed to include the following changes: • Allow 30 days rather than 14 days of drug holiday from enzalutamide treatment prior to initiation enzalutimde as investigational product within the study to ensure sufficient time for completion of pre-screening and screening assessments • Clarify and define the 14-day treatment with enzalutamide monotherapy prior to the addition of GSK263771 as the "Enzalutamide Run-In Period", that the Enzalutamide Run-In Period is to follow completion of pre-screening and screening rather than be concurrent with screening, and other administrative changes needed as a result of defining the Enzalutamide Run-in Period (e.g., specify collection of adverse events [AEs] during the Enzalutamide Run-In Period and that enzaluitmide will be provided during the Enzalutamide Run-In Period) • Added an assessment for genetic research • Add parathyroid hormone assessments at baseline and in the event of Grade 2 or higher hypocalcemia or hypophosphatemia • Add updated standard GlaxoSmithKline protocol language for specific AEs (i.e., liver chemistry stopping criteria). • Removed androgen receptor antagonists from the list of prohibited medications and other changes to lists of medications to avoid or use with caution The remaining changes are largely administrative, and intended to provide additional clarification or to correct inadvertent errors		
2013N172718_03	2016-JUN-24	Amendment No.3
Amendment 3 was completed to update the risk assessment section and to include additional requirements for monitoring of renal events. Optional pharmacodynamics paired biopsies as well as clarifications around biomarker assessments were added to the Time and Events tables for the Dose Escalation and Dose Expansion Phases. Additional		

<table>
<tr><td colspan="3">language was added to clarify that:
Subjects with disease progression defined by PSA progression alone or for the worsening of an isolated disease site that is not clinically significant are not required to discontinue treatment in the study,
The decision to terminate the Dose Expansion Phase will take into account all relevant factors, including but not soley based upon the statistical methodogy and futility criterion.
Other minor clarifications were also added.</td></tr>
<tr><td>2013N172718_04</td><td>2017-JAN-27</td><td>Amendment No. 4</td></tr>
<tr><td colspan="3">Amendment 4 was completed to include the following:
Additional requirements for monitoring of events related to calcium results. This includes revisions to the Table & Events to clarify additional laboratory testing requirements
Clarification of secondary clinical activity endpoints and update to associated statistical section(s)
Revision of clinical activity population to allow analyses to occur using a combination of dose escalation and dose expansion populations
Revision of dose escalation and dose expansion wording to move into dose expansion with a MTD or lower dose level and to clarify that multiple dose levels may be examined in the dose expansion phase to establish RP2D after dose expansion phase
Adjustment to Week 12 visit window to assist correct timing of disease assessments for this visit after actual 12 weeks on combination treatment
Revision to reflect current indication for enzalutamide throughout the document
Clarification of study populations
Clarification of bone progression definition
Other minor clarifications and corrections of inadvertent errors were also added</td></tr>
</table>

SPONSOR SIGNATORY

PPD

Jan 27, 2017

Date

Li Yan, MD PhD

VP, Head Unit Physician Oncology

PPD

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Regulatory Agency Identifying Numbers:

Investigational New Drug (IND) No:	113058
EudraCT No:	2013-005111-27

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol 200331

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS

°C	Degrees Celsius
°F	Degrees Fahrenheit
ADP	Adenosine diphosphate
AE	Adverse Event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Androgen receptor
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the concentration-time curve
AUC(0-t)	Area under the concentration-time curve from zero over the dosing interval
AUC(0-τ)	Area under the concentration-time curve from zero to the last quantifiable blood or plasma concentration
AUC(0-24)	Area under the concentration-time curve from zero (pre-dose) to 24 hrs
BBB	Bundle branch block
BCRP	Breast cancer resistant protein
BP	Blood pressure
BUN	Blood urea nitrogen
C24	Trough concentration
CBC	Complete blood count
cfDNA	Circulating-free tumor DNA
CI	Confidence Interval
CL/F	Oral clearance
Cmax	Maximum observed concentration
CO_2	Carbon dioxide
CR	Complete response
CRPC	Castrate-resistant prostate cancer
CSR	Clinical study report
CT	Computed tomography
CTA	Clinical Trial Application
CTC	Circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DHT	Dihydrotestosterone
DILI	Drug induced liver injury
dL	Deciliter
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECHO	Echocardiogram

ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
Emax	Maximum effect
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose-positron emission tomography
FISH	Fluorescent in situ hybridization
ft	Foot
FTIH	First time in human
g	Gram
GCP	Good Clinical Practice
GI	Gastrointestinal
GnRH	Gonadotropin releasing hormone
GSK	GlaxoSmithKline
h/hr	Hour(s)
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HPLC	High performance liquid chromatography
IB	Investigator's Brochure
IBW	Ideal body weight
ICF	Informed consent form
ICH	International Conference on Harmonization
IDSL	International Data Standards Library
IEC	Independent Ethics Committee
IgG or M	Immunoglobulin G or M
IHC	Immunohistochemistry
IMP	Investigational medicinal product
IND	Investigational New Drug
INPP4B	Inositol polyphosphate-4-phosphatase type II
INR	International Normalized Ratio
IP	Investigational product
IR	Immediate release
IRB	Institutional Review Board
IV	Intravenous
ka	Absorption rate constant
kg	Kilogram
L	Liter
LCH	Langerhans cell histiocytosis
LDH	Lactate dehydrogenase
LHRH	Luteinizing hormone releasing hormone
LLN	Lower limit of normal
LOH	Loss of heterozygosity
LVEF	Left ventricular ejection fraction
M	Mandatory
MCH	Mean corpuscular hemoglobin
mCRPC	Metastatic castration-resistant prostate cancer

MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Milliliter
mm	Millimeter
mmHg	Millimeters of mercury
mmol	Millimolar
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MSDS	Material Safety Data Sheet
msec	Milliseconds
MTD	Maximum tolerated dose
mTOR	Mammalian Target of Rapamycin
MUGA	Multigated acquisition scan
N, n	Number
NA	Not available or not applicable
NE	Not evaluable
ng	Nanogram
NLCB	No longer clinically benefitting
nM	Nanomolar
NYHA	New York Heart Association
O	Optional
OATP	Organic anionic transferase peptide
OCT	
ORR	Objective Response Rate
OTC	Over-the-counter
P-gp	P-glycoprotein
pAKT	Phosphorylated AKT
PCR	Polymerase chain reaction
PCWG2	Prostate Cancer Working Group 2
PCWG3	Prostate Cancer Working Group 3
PD	Pharmacodynamic or progressive disease
PET	Positron emission tomography or probability of early termination
Pgp	P-glycoprotein
PHLPP	PH and leukine-rich repeat protein phosphatase (a negative regulator of AKT)
PI3K	Phosphoinositide 3-kinase
PI3KCA	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
PI3KR1	Phosphoinositide-3-kinase, regulatory subunit 1 (alpha)
PI3KR3	Phosphoinositide-3-kinase, regulatory subunit 3 (gamma)
PI3Kβ	Phosphoinositide 3-kinase beta
PK	Pharmacokinetic
PR	Partial response
PRP	Platelet rich plasma
PSA	Prostate-specific antigen
PSA50	Prostate-specific antigen decrease from baseline ≥50%

PT	Prothrombin time
PTEN	Phosphatase and tensin homolog
PTH	Parathyroid hormone
PTS-DMPK	Platform Technology and Science – Drug Metabolism and Pharmacokinetics
PTT	Partial thromboplastin time
QTc	Corrected QT interval
QTcB	QT interval corrected by Bazett's formula
QTcF	QT interval corrected by Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase II dose
rPFS	Radiological progression free survival
RR	Response rate
SAE	Serious adverse event(s)
SBP	Systolic blood pressure
SD	Stable disease or standard deviation
SRM	Study Reference Manual
t1/2	Half-life
Tmax	Time of occurrence of maximum observed concentration
TMF	Trial Master File
UGT	UDP-glucuronosyltransferase
UK	United Kingdom
ULN	Upper limit of normal
UPC	Urine protein to creatinine
US	United States
V/F	Oral volume of distribution
WBC	White blood cells
Wk(s)	Week(s)
WNL	Within normal limits
Yr	Year

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PROTOCOL SYNOPSIS

TITLE	A Phase I, Open-Label, Dose-Finding Study of GSK2636771 Administered in Combination with Enzalutamide (Xtandi) in Male Subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC)
PROTOCOL NUMBER	200331
CLINICAL PHASE	I
COMPOUND	GSK2636771
STUDY RATIONALE	Despite recent advances in the treatment of advanced prostate cancer, relapses are inevitable and metastatic castration-resistant prostate cancer (mCRPC) carries considerable morbidity along with shortened survival. Previous studies have indicated the importance of the phosphoinositide 3-kinase (PI3K) pathway in prostate cancer. A common event in prostate cancer progression is the loss of tumor suppressor phosphatase and tensin homolog (PTEN) in 40-50% of mCRPC patients that results in the activation of the PI3K pathway. The choice of subject populations represented in this study is based on the hypothesis that activation of the PI3K pathway in mCRPC will result in increased sensitivity to the combination and thus subjects will be selected on the basis of PTEN deficiency. Therapeutic approaches that simultaneously inhibit both the androgen receptor (AR) pathway and the PI3K pathway may be more effective than inhibition of either pathway alone in mCRPC. Enzalutamide is an AR inhibitor indicated for the treatment of patients with mCRPC. The proposed Phase I study will evaluate the safety and tolerability, pharmacokinetics (PK), and clinical activity to determine the recommended Phase II dose (RP2D) and regimen of GSK2636771 in combination with enzalutamide given orally in adult male subjects with mCRPC.
STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESES	**Primary Hypothesis:** The addition of a targeted PI3K pathway inhibitor (GSK2636771) to enzalutamide treatment can be safely administered with ongoing enzalutamide treatment. **Secondary Hypothesis:** The addition of a targeted PI3K pathway inhibitor (GSK2636771) to enzalutamide can limit mCPRC progression in a clinically meaningful way for at least 12 weeks. The null hypothesis is that the 12-week non-progressive disease (PD) rate is not attractive (≤5%). The alternative hypothesis is that the rate is clinically meaningful and, therefore, the compound warrants further development (≥30%). This hypothesis will be tested for Part 2 of the study, combining eligible subjects from Part 1.

STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESES *continued*

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of GSK2636771 + enzalutamide administered orally once daily continuously in subjects with mCRPC.	• Adverse Events (AE), Serious Adverse Events (SAE), Dose Limiting Toxicities (DLTs), and changes in laboratory values, Electrocardiograms (ECGs), and vital signs (Blood Pressue [BP], temperature and heart rate)
• To determine the RP2D of orally administered GSK2636771 + enzalutamide in subjects with mCRPC.	• Safety and tolerability as assessed by AEs, SAEs, DLTs, and changes in laboratory values, ECGs, and vital signs (BP, temperature and heart rate)
• To evaluate lack of progression in the dose expansion subjects with mCPRC by rate of subjects who do not progress for 12 weeks	• Non-PD rate for 12 weeks according to PCWG2 criteria (either by Response Evaluation Criteria In Solid Tumors [RECIST] 1.1, or progression in bone or Prostate Specific Antigen [PSA] progression with accompanying progression by RECIST 1.1 or bone scan when baseline radiological or bone disease present or PSA progression if no other baseline disease).
Secondary	
• To evaluate the clinical activity of oral GSK2636771 + enzalutamide in the treatment of mCRPC (PTEN deficient)	• PSA50 response rate defined as the percent of subjects achieving PSA50 at 12 weeks or thereafter (PSA50 is ≥50% decrease in PSA from baseline) • Objective Response Rate (ORR) defined as complete response (CR) rate plus partial response (PR) rate per RECIST 1.1 • Time to PSA progression according to PCWG2 criteria

STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESES
continued

	• Time to radiological progression according to PCWG2 criteria (either by RECIST 1.1, and/or progression in bone) • Radiological progression free survival (rPFS) per RECIST1.1 and/or bone scans
• To determine the effect of GSK2636771 on enzalutamide PK following repeat-dose oral administration.	• Plasma concentrations of enzalutamide and N-desmethyl enzalutamide.
• To determine the PK of GSK2636771 in the presence of enzalutamide.	• Blood GSK2636771 concentrations.
Exploratory	
• To determine the frequency of PTEN deficiency in subjects with mCRPC	• Frequency of PTEN-deficient mCRPC reported in subjects based on pre-screened tumors
• To determine the mechanism of PTEN deficiency	• PTEN deletion, mutation or promoter methylation
• To identify additional biomarkers (DNA, RNA or protein based) in tumor or in circulation that may predict response to oral GSK2636771 + enzalutamide	• Response prediction biomarkers based on analysis of DNA, RNA, and proteins from surrogate tissues (e.g., cfDNA) and/or tumor tissue
• To determine the effect of enzalutamide with GSK2636771 on the kinetics of tumor growth	• Longitudinal tumor size measurements; serum PSA levels, change from baseline in CTCs
• Evaluation of biomarkers in CTCs that may predict response to combination	• AR expression, PTEN FISH and other genomic evaluations in CTCs
• Evaluation of tumor tissue to explore explanation for the mechanism of resistance to combination therapy	• Based on analysis of DNA, RNA and proteins from tumor tissue obtained at time of progression after initially responding to combination therapy
• To determine pharmacodynamic effects of drug treatment	• RNA/protein analysis of pre/post treatment tumor biopsies

Abbreviations: AEs, adverse events; AR, androgen receptor; BP, blood pressure; cfDNA, circulating-free deoxyribonucleic acid; CTC, circulating tumor cells; DLTs, dose limiting toxicities; DNA, deoxyribonucleic acid; ECG, electrocardiogram; FISH, fluorescent in situ hybridization; mCRPC, metastatic castration-resistant prostate cancer; PCWG2, Prostate Cancer Working Group 2; PD, progressive disease; PK, pharmacokinetics; PSA, prostate-specific antigen; PTEN, phosphatase and tensin homolog; RECIST, Response Evaluation in Solid Tumors; RNA, ribonucleic acid; RP2D, recommended Phase II dose; SAE, serious adverse event(s)

STUDY DESIGN

This is a Phase I, open-label, non-controlled, non-randomized, dose-finding, multicenter study to determine the RP2D of the oral PI3K beta (PI3Kβ) inhibitor, GSK2636771 in combination with enzalutamide in subjects with mCRPC.

Pre-Screening and Screening: Subjects will be required to undergo pre-screening to determine the PTEN status of their tumor. Details regarding the PTEN requirements are provided in the Study Reference Manual. Subjects will sign a separate Informed Consent Form (ICF) to allow for pre-screening of archived tumor tissue or tumor tissue from a fresh tumor biopsy.

Subjects will be required to sign another ICF for the main study at Screening prior to initiation of any screening procedures or assessments. Screening assessments will be conducted to determine subject eligibility for enrollment into the study.

Dose Escalation Phase

Enzalutamide Run-In Period (Days 1-14): Approximately 24 subjects will be enrolled in the 14-day run-in period and receive enzalutamide monotherapy at the approved dose of 160 mg once daily.

Combination Treatment Period (Weeks 1-4): Subjects who complete the Enzalutamide Run-In Period will begin oral GSK2636771 treatment on Week 1, Day 1 of the Combination Treatment Period while continuing to receive enzalutamide to evaluate safety of the combination therapy.

The combination dose will be studied following a 3+3 dose modification procedure. Additional doses may be explored based upon ongoing assessment of safety and PK. Dose escalation decisions will be made utilizing all available data at the end of the Dose Limiting Toxicity (DLT) reporting period (the first 28 days of combination treatment).

The starting dose of GSK2636771 is 300 mg once daily. The enzalutamide dose will remain fixed at 160 mg once daily. Additional dose levels of each study treatment may be explored based upon ongoing assessment of safety and PK. Dose modification decisions will be made utilizing all available safety and PK data at the end of the DLT reporting period (the first 28 days of combination treatment).

A minimum of 3 subjects may be enrolled in each subsequent cohort until the maximum tolerated dose (MTD) is defined. Evaluation of at least 3 subjects

STUDY DESIGN ***continued***

who have completed 28 days of combination treatment is required prior to dose escalation to the next cohort. Dose escalation will proceed with the increment of the GSK2636771 dose increase determined by toxicity rules.

3+3 Dose Escalation Guidelines Based on Toxicity

Number of Subjects with a DLT	Action
0 out of 3 subjects	Escalate to next dose level.
1 out of 3 subjects	Accrue 3 additional subjects at current dose level for a total of 6 subjects
1 out of 6 subjects	Escalate to the next dose level.
2 or more subjects in a dosing cohort (up to 6 subjects)	Dose escalation will be stopped. At this dose level, the MTD has been exceeded (highest dose administered). Either evaluate at a lower intermediate dose (3+3 dosing) or expand a prior cohort up to approximately 20 subjects per treatment arm.

Abbreviations: DLT, dose limiting toxicity; MTD, maximum tolerated dose

If the combination doses in Cohort 1 are not tolerable, lower doses as defined in the de-escalation cohort (Cohort -1) will be evaluated. If the de-escalation cohort (Cohort -1) is not tolerable, further dose escalation using a continuous daily dosing schedule for both compounds simultaneously will be terminated.

Dose escalation will proceed until the MTD of the combination regimen is identified. If the dose(s) administered to a given cohort exceeds the MTD, intermediate doses may be explored. Dose escalation decisions will take into account all available data, including the safety profile and PK data of prior cohorts throughout the time subjects are on study, which will be reviewed by the investigator(s), GlaxoSmithKline (GSK) Medical Monitor, pharmacokineticist and statistician. In the absence of DLTs, the dose of GSK2636771 may be escalated to the MTD of 400 mg as determined in the first-time-in-human study (P3K115717).

If diarrhea (in the absence of aggressive diarrhea management), fatigue or rash defines the MTD, the cohort in which the toxicity is observed may be expanded by at least 3 subjects and the efficacy of supportive care evaluated prior to further dose escalation. If supportive care measures ameliorate the toxicity without recurrence of the toxicity, further dose escalation may be conducted in the presence of appropriate supportive care.

Treatment Continuation Period (Week 5 and thereafter): Subjects will continue to receive the combination treatment of GSK2636771 + enzalutamide until criteria are met for discontinuation of study treatment.

STUDY DESIGN
continued

Dose Escalation Cohorts

Cohort	N	GSK2636771	Enzalutamide
-1	3 - 6	200 mg once daily	160 mg once daily
1	3 - 6	300 mg once daily	160 mg once daily
2	3 - 6	400 mg once daily	160 mg once daily

Cohort Expansion: Selected dose levels may enroll up to 12 additional subjects to ensure a sufficient number of subjects enrolled to assess PK and/or safety. The MTD may be the recommended dose combination for future Phase II studies unless there is a lower dose of GSK2636771 that provides adequate PK exposure and biologic activity with superior tolerability. The final decision will be based on the totality of data.

Alternate dose levels and schedules may also be explored based on emerging safety, PK or PD data.

Definition of DLT: An event will be considered a DLT if the event is attributed (definitely, probably or possibly) to study treatment, occurs within the first 28 days of combination treatment (DLT reporting period), and meets one of the following criteria:

- Grade 3 or greater non-hematologic toxicity that cannot be controlled with routine supportive measures (e.g., anti-emetics, anti-diarrheals)
- Grade 4 neutropenia lasting >5 days
- Febrile neutropenia, of any grade or duration as defined by Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0)
- Grade 4 thrombocytopenia
- Alanine aminotransferase (ALT) ≥3 times upper limit of normal (ULN) (or ALT ≥3 times ULN and ≥1.5 times baseline ALT value, if enrolled with liver metastases/tumor infiltration at baseline) and bilirubin ≥2 times ULN

Any Grade 2 or greater toxicity per CTCAE v4.0 that that occurs beyond the 28-day DLT reporting period which in the judgment of the investigator and GSK Medical Monitor would be considered dose limiting

NOTE: Subjects who fail to receive at least 75% of protocol-specified study treatment during the DLT reporting period (the first 28 days of combination treatment), for reasons OTHER than toxicity, will be replaced if data from the

replacement subject could impact the dose selection criteria.

STUDY DESIGN ***continued***

Subjects who experience an intolerable toxicity causing a dose interruption or dose reduction during the Enzalutamide Run-In Period (before the start of GSK2636771 combination treatment) will require approval from the GSK Medical Monitor in order to continue in the study. Those subjects not eligible for treatment in the Combination Treatment Period will not be considered in the evaluation of DLTs and may be replaced.

Dose Expansion Phase

This phase of the study will evaluate the long term safety of the combination treatment as well as the 12-week non-progressive disease (PD) rate of the combination treatment in subjects with mCPRC. To confirm dose(s) identified during dose escalation, multiple dose levels of GSK2636771 in combination with enzalutamide may be examined during dose expansion, with each dose level cohort enrolling up to 20 subjects. Using the totality of safety, PK and clinical activity data, the RP2D will be confirmed from the dose level(s) which are examined in the dose expansion phase.

Enzalutamide Run-In Period (Days 1-14): Following pre-screening and screening, approximately 20 subjects will be enrolled and receive enzalutamide monotherapy at the approved dose of 160 mg once daily for 14 days.

Combination Treatment Period (Weeks 1-4): Subjects who complete the Enzalutamide Run-In Period will begin oral GSK2636771 treatment on Week 1, Day 1 of the Combination Treatment Period at the RP2D dose established in the Dose Escalation Phase of the study while continuing to receive enzalutamide to evaluate safety of the combination therapy.

Treatment Continuation Period (Week 5 and thereafter): Subjects will continue to receive the combination treatment of GSK2636771 + enzalutamide until criteria are met for discontinuation of study treatment.

PK: Blood and plasma samples for PK analysis of GSK2636771 and enzalutamide (including its active metabolite, N-desmethyl enzalutamide) will be collected on specified PK days in the Dose Escalation and Dose Expansion Phase.

Genetic Research: A single blood sample will be collected after Screening, preferably on Week 1, Day 1 of the Combination Treatment Period, if informed consent has been obtained for genetic research.

NUMBER OF SUBJECTS

A total of approximately 44 to 64 subjects will be enrolled in this study.

In the Dose Escalation Phase, the number of dose levels and the level at which the MTD is reached cannot be determined in advance. An adequate number of subjects will be enrolled to establish the MTD. It is estimated that approximately 24 subjects will be enrolled to allow assessment of safety and preliminary efficacy in PTEN-deficient mCRPC with disease progression on

enzalutamide.

In the Dose Expansion Phase, it is estimated that approximately 20 subjects will be enrolled, with evaluation for futility after the first 10 subjects have completed 12 weeks of treatment. This analysis may occur using the combination of the dose escalation and dose expansion population. If multiple dose levels of GSK2636771 are examined during dose expansion to establish the RP2D, each dose level cohort will enrol approximately 20 subjects, increasing the overall number of subjects targeted for enrolment in this study. The sample size planned for the Dose Expansion Phase is not driven by statistical considerations as the cohort is meant to further understand the safety implications of enrolling subjects to combination therapy for an extended period of time.

INCLUSION/ EXCLUSION CRITERIA

Key Inclusion Criteria

1. Signed written informed consent provided

   NOTE: Separate ICFs must be signed prior to the pre-screening and screening procedures.

2. Males ≥18 years of age (at the time written consent is obtained for pre-screening)
3. Histologically or cytologically confirmed diagnosis of prostate adenocarcinoma, surgically castrated or continuous medical castration (for ≥8 weeks prior to Screening)
4. Serum testosterone <50 ng/dL (1.7 nM/L)
5. PTEN-deficient tumor as documented from archived or fresh (from pre-treatment biopsy) tumor tissue analyzed by a GSK selected laboratory
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
7. Has completed at least 12 weeks of prior continuous therapy with enzalutamide
8. Has not been without enzalutamide treatment for >30 days prior to enrollment
9. Has documented disease progression following treatment with enzalutamide at time of Screening

   NOTE: Disease progression is defined by one or more of the following criteria:

   - PSA progression defined by PCWG2 criteria (see Section 8.8.2.1), or
   - Soft tissue disease progression defined by RECIST 1.1 (see Appendix 4), or
   - Bone disease progression defined by PCWG2 criteria (see

INCLUSION/ EXCLUSION CRITERIA *continued*

Section 8.8.2.2)

10. Able to swallow and retain orally administered medication.
11. Adequate baseline organ function at time of Screening defined as:

Hematologic	
ANC	*≥1.5 x 10^9/L*
Hemoglobin	*≥9 g/dL*
Platelets	*≥100 x 10^9/L*
PT/INR and PTT	≤1.3 x ULN
Hepatic	
Albumin	≥2.5 g/dL
Total bilirubin[1]	≤1.5 x ULN
AST	≤2.5 x ULN
ALT[1]	≤2.5 x ULN or >2.5 x ULN but ≤5 x ULN with documented liver metastases or tumor infiltration
Renal	
Urine Protein (via dipstick)[2]	0/+1
UPC[3,4]	<0.2
Serum Creatinine	≤ULN
OR	
Estimated Serum Creatinine Clearance[5]	≥60 mL/min
OR	
24-hr Urine Creatinine Clearance	≥60 mL/min
Cardiac	
LVEF	≥50% by ECHO or MUGA
Other	
Serum Phosphate	WNL
Serum Calcium[6] (corrected)	WNL
Ionized Calcium[6]	WNL
Vitamin D[6]: 25-OH D and 1,25-OH2 D	WNL

Abbreviations: ANC, absolute neutrophils count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; ECHO, echocardiogram; INR, international normalization ratio; LLN, lower limit of normal; LVEF, left ventricular ejection fraction; MUGA, multigated acquisition scan; PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; UPC, urine protein to creatinine ratio; WNL, within normal limits

1. If ALT or bilirubin values are outside range listed due to Gilbert's syndrome or asymptomatic gallstones, subject remains eligible.
2. If subject's urine protein is >1+ (via dipstick), then UPC ratio will be calculated. Subject will be considered eligible for study if UPC ratio is <0.2.
3. UPC ratio is only to be calculated if subject's urine protein is >1+ via dipstick.
4. The UPC value will not be used to determine eligibility for subjects who are unable to obtain uncontaminated urine samples due to their disease.
5. Estimated by the CKD-EPI equation (see Appendix 3)

6. Vitamin D supplementation may be added to achieve values WNL. Calcium supplements should be added for subjects with calcium values near the lower normal limit.

NOTE: Laboratory results obtained during Screening should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the investigator may opt to retest the subject and the subsequent within range screening result may be used to confirm eligibility.

12. Male subject with a female partner of childbearing potential or pregnant must agree to use two acceptable methods of contraception from time of Screening until 3 months after the last dose of study treatments (see Section 11.1).

INCLUSION/ EXCLUSION CRITERIA ***continued***

Key Exclusion Criteria

1. Prior treatment with:

   - Anti-cancer therapy (e.g., chemotherapy with delayed toxicity, immunotherapy, biologic therapy or chemoradiation) within 21 days (or within 42 days if prior nitrosourea or mitomycin C containing therapy) prior to enrollment and/or daily or weekly chemotherapy without the potential for delayed toxicity within 14 days prior to enrollment

     Exception: Subjects may remain on luteinizing hormone releasing hormone (LHRH) agonists (i.e., leuprolide, goserelin, triptorelin or histrelin) and AR antagonists (e.g., bicalutamide, flutamide, nilutamide; but not abiraterone).

     Exception: Subjects must have received prior treatment with enzalutamide.

   - Any PI3K, AKT or mammalian target of rapamycin (mTOR) inhibitors
   - Investigational drug(s) (other than enzalutamide) within 30 days or 5 half-lives, whichever is longer, prior to enrollment

2. Prior malignancy other than CRPC.

   Exception: Subjects who have been disease-free for 5 years, or subjects with a history of completely resected non-melanoma skin cancer or successfully treated *in situ* carcinoma are eligible.

3. Current use of or anticipated requirement during the study of any prohibited medication(s) (see Section 10.2)

4. Any unresolved ≥Grade 2 toxicity (per CTCAE 4.0) from previous anti-cancer therapy at time of enrollment, except alopecia or Grade 2 anemia (if hemoglobin is >9.0 g/dL)

5. Presence of any clinically significant GI abnormality or other condition(s) that may alter absorption such as malabsorption syndrome or major resection of the stomach or substantial portion of the small intestine

   NOTE: If clarification is needed as to whether a GI abnormality,

INCLUSION/ EXCLUSION CRITERIA ***continued***

condition or resection will significantly affect the absorption of study treatment, contact the GSK Medical Monitor.

6. Active peptic ulcer disease or history of abdominal fistula, GI perforation, or intra- abdominal abscess within 28 days prior to enrollment
7. Previous major surgery within 28 days prior to enrollment
8. Known active infection requiring intravenous (IV) or oral anti-infective treatment
9. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at time of Screening or within 3 months prior to enrollment
10. A positive pre-study drug/alcohol screening (testing at time of Screening is not required).
11. A positive test for human immunodeficiency virus (HIV) antibody (testing at time of Screening is not required).
12. Evidence of severe or uncontrolled systemic diseases (e.g., unstable or uncompensated respiratory, hepatic, renal or cardiac disease)
13. History of seizure or any condition that may predispose subject to seizure (e.g., prior cortical stroke or significant brain trauma).
14. History of loss of consciousness or transient ischemic attack within 12 months prior to enrollment
15. Has a QTc >450 msec or QTc >480 msec for subjects with bundle branch block (BBB)

    NOTES: The QTc is the QT interval corrected for heart rate by Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read.

    The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial.

    For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).
16. History or evidence of cardiovascular risk including any of the following:
    - Clinically significant ECG abnormalities including second degree (Type II) or third degree atrioventricular block
    - History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, stenting, or bypass grafting within the past 6 months prior to enrollment

INCLUSION/ EXCLUSION CRITERIA *continued*

- Class III or IV heart failure as defined by the NYHA functional classification system (Appendix 2)
- Left ventricular ejection fraction (LVEF) below 50%
- Known cardiac metastases

17. Poorly controlled hypertension (defined as systolic blood pressure [SBP] of ≥150 mmHg or diastolic blood pressure [DBP] of >100 mmHg based on a mean of three measurements at approximately 2-minute intervals)

    NOTE: Initiation or adjustment of antihypertensive medication(s) is permitted if done 30 or more days prior to enrollment.

18. History of congenital platelet function defect (e.g., Bernard-Soulier syndrome, Chediak-Higashi syndrome, Glanzmann thrombasthenia, storage pool defect)
19. Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GSK2636771or enzalutamide or excipients.
20. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures.
21. Exposure to more than 4 investigational medicinal products (IMPs) within 12 months prior to enrollment

STUDY TREATMENT DOSE/ROUTE/ REGIMEN

The planned starting dose of study treatment will be GSK2636771 300 mg orally once daily in combination with enzalutamide 160 mg orally once daily.

Additional doses of each study treatment regimen may be explored based upon ongoing assessment of safety, PK or PD.

SAFETY ASSESSMENTS

Safety assessments will include physical examination, vital signs, ECOG performance status, 12-lead ECGs, echocardiogram/multigated acquisition scan and monitoring for AEs.

The following clinical laboratory tests will be conducted:

Hematology: platelet count, red blood cell (RBC) count with RBC indices, white blood cell (WBC) count with automated WBC differential, hemoglobin, hematocrit and reticulocyte count.

Clinical chemistry: blood urea nitrogen, creatinine, glucose (fasting), sodium, potassium, chloride, carbon dioxide, calcium (serum and ionized), vitamin D, aspartate aminotransferase (AST), ALT, alkaline phosphatase, total protein, albumin, uric acid and total/direct bilirubin, phosphorus, and magnesium.

Urinalysis: specific gravity, pH, glucose, protein, blood and ketones by dipstick, and microscopic examination (if blood or protein is abnormal). Urine-protein-creatinine (UPC) will also be included if urine protein is >1+ by

SAFETY ASSESSMENTS ***continued***	dipstick. <u>*Other tests*</u>: PSA, serum testosterone, parathyroid hormone, and coagulation tests (prothrombin time, partial thromboplastin time and international normalization ratio).
PK/PD ASSESSMENTS	**PK:** In the Dose Escalation and the Dose Expansion Phase, blood and plasma samples for PK analysis of GSK2636771 and enzalutamide (including its active metabolite, N-desmethyl enzalutamide) will be collected. Each PK sample should be collected as close as possible to the planned time relative to the dose (i.e., time zero) administered to the subject on specified PK days. **PK Analysis:** Concentrations of GSK2636771 and enzalutamide (including its active metabolite, N-desmethyl enzalutamide) will be determined from blood and plasma samples obtained during PK sampling using currently approved bioanalytical methodology. Once the blood and plasma have been analyzed for GSK2636771 and enzalutamide any remaining blood and plasma may be analyzed for other compound-related metabolites and the results reported under a separate GSK PTS-DMPK protocol. Tumor size assessments, expressed as linear tumor dimensions, will be described as a function of time.
CLINICAL ACTIVITY ASSESSMENT	Disease assessment will be performed every 8 weeks in all subjects. Response will be determined according to the PCWG2 criteria (either by RECIST 1.1, PSA progression, and/or progression in bone). Subjects whose disease responds should have a confirmatory disease assessment(s) performed at least 4 weeks after the date of assessment during which the response was first demonstrated. Disease progression will be defined according to the definitions established in RECIST 1.1 for soft tissue lesions, or progression in PSA or bone lesions per PCWG2 criteria.
TRANSLATIONAL RESEARCH	**Tumor tissue:** Archived tumor tissue or remaining tumor tissue from the sample submitted for PTEN testing will be utilized to identify potential predictive biomarkers (protein, DNA and RNA based markers). If additional tumor tissue is not available, no new biopsy procedure is required for predictive biomarker analysis. Optional progression biopsies for subjects who have initially responded to the combination therapies and then progressed will also be requested. Genetic and protein based biomarkers will be evaluated to understand the mechanism of resistance/progression.

TRANSLATIONAL RESEARCH ***continued***

Circulating Tumor Cells (CTC): Blood will be collected to enumerate CTCs in circulation. The isolated CTCs may also be evaluated for alterations in AR, PTEN or other genes. Additional blood samples will be collected to isolate CTCs using an EPIC Sciences platform and analyzed for RNA expression (e.g. AR variants), protein markers and/or potential genomic alterations (PTEN loss, PIK3CB mutations, AR amplifications, etc.).

Plasma Collection for Circulating-free DNA (cfDNA) and soluble marker analysis: Plasma will be collected and analyzed for circulating DNA or RNA markers related to disease or the PI3K/Ras/Raf/AR pathway. The samples may also be used to analyze soluble markers of immune response or other markers that may predict response. Other biomarkers identified via emerging science relevant to disease or study treatments related pathways will also be evaluated.

STATISTICAL METHODS

Hypothesis:

Dose Escalation Phase: The total number of subjects to be enrolled in the Dose Escalation Phase is not driven by **hypothesis testing.** The sample size of 24 subjects for the Dose Escalation Phase will provide the following 95% Clopper-Pearson confidence interval (CI) for safety events.

Safety Events	Frequency of Safety Events (95% CI)
1	4.2% (0.1% – 21.1%)
2	8.3% (1.0% - 27.0%)
3	12.5% (2.7% - 32.4%)
4	16.7% (4.7% - 37.4%)
8	33.3% (15.6% - 55.3%)
12	50.0% (29.1% - 70.9%)
16	66.7% (44.7% - 84.4%)
20	83.3% (62.6% – 95.3%)
21	87.5% (67.6% - 97.3%)
22	91.7% (73.0% - 99.0%)
23	95.8% (78.9% - 99.9%)

Abbreviation: CI, confidence interval

For the Dose Expansion Phase, clinical activity will be evaluated per dose level if more than one dose is examined (combing data from Dose Escalation Phase). A targeted PI3K pathway inhibitor (GSK2636771) added to enzalutamide will be tested to see if mCPRC progression can be limited in a clinically meaningful way for at least 12 weeks. The null hypothesis is that the 12-week non-PD rate is not attractive (≤5%). The alternative hypothesis is that the rate is clinically meaningful and therefore, the compound warrants further development (≥30%). A maximum of 20 subjects per dose level may be enrolled, with a minimum enrollment of 10 subjects. With an actual type I error rate (α) of 0.065 and 94.2% power, the design has stopping criteria defined for futility as follows.

STATISTICAL METHODS ***continued***

The trial is designed to stop early for futility if the predictive probability of success is less than 6%. The type I error rate, power, and predictive probability of success to stop early for futility were derived from explicitly stating the minimum and maximum sample size, futility stopping rate, and selection of the optimizing criterion as the maximization of power under the alternative hypothesis. The Bayesian prior probability used in determining the design was Beta (0.10, 0.90), a distribution with a mean response rate (defined as lack of disease progression at 12 weeks according to PCWG2 criteria [either by RECIST 1.1, PSA progression, and/or progression in bone]) of 10%. Under the null hypothesis, if the true response rate is 5%, the expected sample size of the design is 13.1 subjects and probability of early termination (PET) is 83.0%. Under the alternative hypothesis, if the true response rate is 30%, the expected sample size of the design is 19.7 subjects and PET is 4.3%.

Number of Subjects Enrolled	≤ This Number of Responses[1] to Stop Early for Futility
10	0
11	0
12	0
13	0
14	0
15	0
16	1
17	1
18	1
19	1
20	2

Abbreviation: PCWG2, Prostate Cancer Working Group 2

1. Response for the purpose of futility is defined as lack of disease progression at 12 weeks according to PCWG2 criteria. PSA progression in subjects with baseline radiological or bone disease will require RECIST or bone progression in addition to PSA progression to be determined a disease progressor.

Study Populations:

The **All Treated Safety Population** is defined as all subjects who receive at least one dose of GSK2636771 or Enzalutamide. Safety will be evaluated based on this analysis population.

The **All Treated Clinical Activity Population** is defined as all subjects who received at least one dose of GSK2636771. Clinical activity and evaluation of non-PD rate will be based on this analysis population. This will include subjects from both dose escalation and dose expansion.

The **All Evaluable Population** is defined as all subjects from All Treated Clinical Activity Population who have at least one post-dose disease assessment and have been exposed to study drug for at least 12 weeks or have progressed or have died or have withdrawn from the study for any

STATISTICAL METHODS ***continued***

reason. Dose Expansion futility analyses will be based on this population.

The **PK Population** will consist of all subjects from the All Treated Population for whom at least one PK sample is obtained and analyzed.

Efficacy Analyses: The All Treated Clinical Activity Population will be used for the analysis of efficacy data, and will be summarized separately per dose level. Response data per PCWG2 and RECIST 1.1 guidelines will be reported. Further details about efficacy analyses will be outlined in detail in the RAP.

Safety Analyses: The All Treated Safety Population will be used for the analysis of safety data. All serially collected safety endpoints (e.g., laboratory tests, vital signs, ECGs) will be summarized according to the scheduled, nominal visit at which they were collected and across all on-treatment time points using a “worst-case” analysis.

Additional details of the statistical analysis plan will be provided in the RAP.

1. INTRODUCTION

1.1. Metastatic Castration-Resistant Prostate Cancer

Prostate cancer is the most frequently diagnosed cancer among men and the second-leading cause of cancer-related death in men [American Cancer Society, 2013]. Over the past decades the primary target of treatment has been focused on depleting or blocking androgen activity as the growth of prostate cancer is dependent on androgens. Hormonal therapy has included the use of gonadotropin-releasing hormone (GnRH) analogues, androgen receptor (AR) antagonists, ketoconazole and estrogenic compounds. Despite early sensitivity to hormonally directed therapies and while maintaining castrate levels of serum testosterone, these tumors often eventually progress as castration-resistant prostate cancer (CRPC). Once metastatic CPRC (mCPRC) develops, the mean survival time in these patients is approximately 16 to 18 months [Karantanos, 2013].

The AR signaling axis frequently remains active despite castration therapy in CRPC, as is clinically evident by the rise in prostate-specific antigen (PSA) and hypersensitivity to even low levels of residual androgens, suggesting that continued treatment directed at the AR signaling axis may provide benefit. Overexpression of AR is seen in over 50% of CRPC and is thought to be a significant contributor to progression. Despite recent advances in the development of therapeutic options (e.g., abiraterone acetate, enzalutamide, etc.), disease progression is inevitable and is seen in the form of resistant tumors with PSA expression that suggests an active AR axis.

The phosphoinositide 3-kinase (PI3K)-AKT pathway is among the most commonly activated pathways in human cancer and is active in the majority of metastatic prostate cancer [Taylor, 2010; Bitting, 2013]. Activation of the PI3K-AKT pathway can occur due to several different aberrations: decreased expression of the inhibitory phosphatase and tensin homolog (PTEN), inositol polyphosphate-4-phosphatase type II (INPP4B), and pH and leukine-rich repeat protein phosphatase (PHLPP; a negative regulatory of AKT); activating mutations in the PI3K catalytic gene phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA); and decreased expression of the PI3K regulatory genes phosphoinositide-3-kinase regulatory subunit 1 (PI3KR1) and phosphoinositide-3-kinase regulatory subunit 3 (PI3KR3) [Taylor, 2010]. Loss of PTEN protein is observed in 40 to 50% of mCRPC tumors. Both PTEN loss per se and AKT activation regardless of mechanism have been associated with poor clinical outcome [Yoshimoto, 2008] and recurrence following radical prostatectomy [Ayala, 2004; Bedolla, 2007].

Cross-talk between AR and PI3K-AKT pathways has been observed in models of CRPC as evidenced by activation of AKT signalling with AR inhibition [Carver, 2011]. Conversely, AR transcriptional activity is decreased in PTEN-deficient tumor cells and increased by pharmacological inhibition of PI3K-AKT pathway [Carver, 2011; Martin, 2010].

The concurrent interruption of the AR and PI3K pathways by the combination of enzalutamide with GSK2636771 may provide additive benefit by limiting prostate tumor growth and the development or reversal of AR resistance to enzalutamide.

1.2. GSK2636771

GSK2636771 is a potent, orally bioavailable, adenosine triphosphate (ATP) competitive inhibitor of the PI3Kβ isoforms. It inhibits anchorage-independent growth of the majority of PTEN-deficient, but not PTEN wild-type tumor cell lines. In a PTEN-negative human prostate cancer xenograft mouse model, treatment results in dose-dependent inhibition of AKT phosphorylation and stable disease or tumor growth delays.

A detailed summary of *in vitro* and *in vivo* non-clinical pharmacology studies is provided in the GSK2636771 Investigator Brochure (IB) [GlaxoSmithKline Document Number 2011N117133_01].

1.2.1. Clinical Safety, Pharmacokinetic Data, and Clinical Activity of GSK2636771

To date, the administration of GSK2636771 has been limited to subjects with PTEN deficient tumor as determined by immunohistochemistry (IHC) analysis who were enrolled in the first-time-in-human (FTIH) study P3B115717. Doses of GSK2636771 evaluated have ranged from 25 mg to 500 mg once daily. The maximum tolerated dose (MTD) has been defined as 400 mg orally once daily. Dose-limiting toxicities (DLTs) observed were hypophosphatemia and hypocalcemia. This study is completed and enrolled 65 subjects.

Dose-limiting toxicity (DLT) of hypophosphatemia was identified at 500 mg daily dose level, occurring in 3 of 4 subjects, and resulting in dose reductions and or discontinuations. The hypophosphatemia improved upon discontinuation of GSK2636771. The mechanism(s) of hypophosphatemia is under investigation.

Safety. The most frequent adverse events (AEs) with GSK2636771 were Grade 1 or Grade 2 gastrointestinal (GI) toxicities, with the most frequently reported AEs being diarrhea (42%), nausea (40%), fatigue (30%), vomiting (30%), abdominal pain (26%), decreased appetite (23%), anemia (21%), constipation (17%), headache (17%), hypokalemia (15%), cough (13%), dyspnea (13%), edema peripheral (13%), and urinary tract infection (11%).

Pharmacokinetics. Preliminary pharmacokinetic (PK) results from study P3B115717 indicate that GSK2636771 is absorbed orally with a median time to achieve the peak blood concentration (Tmax) of 4 to 5 hrs after single doses of 25 to 500 mg. The median half-life (t1/2) of GSK2636771 ranged from 17.1 to 38.6 hrs across the dose range of 25 mg to 500 mg once daily. Mean maximum observed concentration (Cmax) and area under the concentration-time curve from zero (pre-dose) to 24 hrs [AUC(0-24)] values on Day 22 were greater than the mean values observed after a single dose, demonstrating that GSK2636771 accumulated in plasma after repeated doses.

Clinical Activity. There are limited data available to assess the clinical activity of GSK2636771. In the FTIH study P3B115717, one subject with mCRPC who received 200 mg GSK2636771 once daily had a partial response (PR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. There were 20 (N=65) subjects who had stable disease, 8 of whom were on study for at least 6 months. Refer to the GSK2636771 IB

[GlaxoSmithKline Document Number 2011N117133_01] for additional details on available safety, PK and clinical activity data.

1.3. Enzalutamide (Xtandi)

Testosterone and its active metabolite dihydrotestosterone (DHT) are normally ligands for AR. Binding to AR causes changes in the composition and conformation, leading to nuclear translocation from the cytoplasmic compartment. Once in the nucleus, the AR binds to androgen response elements on target genes (e.g., PSA) and leads to transcription of messenger ribonucleic acid (mRNA). Traditional androgen deprivation therapy reduces intracellular concentrations of DHT and results in tumor regression in prostate cancer. However, androgen deprivation therapy does not completely inhibit intratumoral androgens or the expression of AR target genes.

The AR is central to the biology of mCRPC. The mechanisms that explain resistance to traditional androgen deprivation therapy include, but are not limited to, AR amplification or point mutations, ligand-independent activation of the AR, and alternative signalling pathways that no longer involve the AR.

Enzalutamide (Xtandi) is an orally bioavailable, AR signalling inhibitor approved in the United States (US) and the European Union for the treatment of patients with mCRPC [Xtandi, 2016]. Enzalutamide acts on several steps in the AR signaling pathway, including competitive inhibition of androgen binding to ARs and inhibition of AR nuclear translocation and its interaction with deoxyribonucleic acid (DNA). A major metabolite, N-desmethyl enzalutamide, exhibited similar *in vitro* activity to enzalutamide.

Refer to to the approved US Food and Drug Administration (FDA) prescribing information [Xtandi, 2016] or the Xtandi Prescribing Information for the area where it is approved for further details.].

1.3.1. Clinical Safety, Pharmacokinetic Data, and Clinical Activity of Enzalutamide

Safety. Generally, treatment with enzalutamide has been well tolerated in subjects with CRPC. Based upon the comparison of safety data from the randomized Phase III study of CRPC subjects treated with enzalutamide 160 mg once daily to placebo, the most common AEs were reported in >5% of subjects: asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equine syndrome, hematuria, paresthesia, anxiety, and hypertension. Grade 3 or higher AEs were reported in 47% of subjects receiving enzalutamide compared to 53% in placebo-treated subjects. The most common AE leading to discontinuation of treatment was seizure.

Seizure is a risk associated with enzalutamide treatment. In a randomized Phase III study of subjects with CRPC, seizures occurred in 7 of 800 (0.9%) enzalutamide subjects (160 mg once daily) compared to no seizures experienced by subjects receiving placebo. The onset of seizures was seen 31 to 603 days from the initiation of treatment. All seizures resolved with discontinuation of enzalutamide. The safety of enzalutamide in

subjects with predisposing factors for seizures has not been evaluated as these subjects were excluded from the study.

Pharmacokinetics. Oral absorption of enzalutamide is rapid and independent of dose with Cmax achieved 1 to 2 hrs post-dose. It is 97 to 98% bound to plasma proteins, primarily albumin. N-desmethyl enzalutamide is 95 to 97% bound to plasma proteins. Enzalutamide is metabolized by CYP3A4 and CYP2C8 to an active metabolite N-desmethyl enzalutamide and primarily eliminated by hepatic metabolism (CYP3A4 and CYP2C8). The mean t1/2 is 5.8 days in patients. With daily administration, steady state is reached after approximately 30 days. In order to achieve near-steady state enzalutamide exposure, a 14-day run-in period has been included in the study design (Section 1.5.3 and Section 3). Enzalutamide accumulates approximately 8.3-fold relative to a single dose with a mean peak-to-trough ratio of 1.25. A high-fat meal did not alter the area under the concentration-time curve (AUC) of enzalutamide or its active metabolite, N-desmethyl enzalutamide.

Clinical Response. In a randomized, double-blinded, Phase III clinical trial comparing enzalutamide with placebo in subjects with mCRPC who had progressed following docetaxel-based chemotherapy, enzalutamide prolonged overall survival by 5 months (median survival of 18.4 months with enzalutamide [n=800] compared to 13.6 months with placebo [N=399]) which is statistically and clinically significant [Xtandi, 2016]. Enzalutamide is approved in the US, Canada, the European Union and others (refer to Xtandi Prescribing Information in the relevant jurisdiction). Recently, enzalutamide has also been shown to improve survival (32.4 months vs. 30.2 months) in chemotherapy-naïve subjects with advanced prostate cancer in a separate Phase III, randomized, placebo-controlled study [Beer, 2014].

Refer to the approved US FDA prescribing information [Xtandi, 2016] or the Xtandi Prescribing Information for the area where it is approved for further details.

1.4. Summary of Risk Management

The risk of administration of GSK2636771 with enzalutamide has not been assessed in clinical trials or in non-clinical toxicology studies. In the placebo-controlled Phase III clinical trial (AFFIRM) of subjects with mCRPC who had received docetaxel therapy, enzalutamide was administered at a dose of 160 mg daily (N = 800) versus placebo (N = 399). The median duration of treatment with enzalutamide was 8.3 months while it was 3.0 months with placebo. Subjects were allowed, but not required, to take prednisone. GSK2636771 has demonstrated activity in solid tumor cell lines. Clinical efficacy data for GSK2636771 in mCRPC are not currently available.

Enrollment criteria and dose modification guidelines will be followed to minimize the risk of identified or potential risks. In the event that any AEs are reported or observed, supportive treatment will be provided according to standard medical practice and/or as specified in the protocol, including dose modification if specified.

Refer to the GSK2636771 IB [GlaxoSmithKline Document Number 2011N117133_01] for detailed information concerning the biology, pharmacology, PK and safety. Refer to

approved US FDA prescribing information [Xtandi, 2016] or the Xtandi Prescribing Information for the area where it is approved for additional information.

1.4.1. Risk Assessment

The assessment of the risk of GSK2636771 combination therapy, and suggestions for management of risk, is based on non-clinical data and clinical data from GSK2636771 monotherapy studies in adults. In the event that any AEs are reported or observed, supportive treatment will be provided according to standard medical practice. Subjects will be withdrawn from the study if a clinically significant toxicity is reported or observed.

1.4.1.1. GSK2636771

Renal and electrolytes: Degenerative changes were observed in the kidneys of rats and dogs at 100 mg/kg/day or 1000 mg/kg/day, including cellular and tubular changes, with chemistry and urinalysis findings. There have been serious, treatment-related reports of acute kidney injury, hypophosphatemia and hypocalcaemia in GSK2636771 clinical trials. Renal events should be closely monitored. It is recommended that patients be well-hydrated and avoid the use of NSAIDs. Calcium and Vitamin D levels will be monitored. Consider supplements in those with calcium levels at or near the lower normal limit and those with low Vitamin D levels. Medical history will be collected and, physical examination and clinical laboratory tests will be measured frequently during therapy to monitor for potential toxicity. Guidelines will be implemented including dose modification and discontinuation (Section 7.3.1) for the management of renal insufficiency, renal-related events or electrolyte abnormalities considered to be related to study treatment.

Gastrointestinal (GI) toxicity: Data from rats receiving GSK2636771 showed microscopic focal erosions or ulcerations in the stomach at 1000 mg/kg/day. Grade 3 treatment-related nausea and vomiting and non-serious diarrhea have been observed in the FTIH study (P3B115717). Eligibility criteria will exclude any subject with active peptic ulcer disease (see Section 4.1.3). Medical history, physical examination and clinical laboratory assessments will be used to identify and assess toxicity in the GI tract. Supportive therapy will be provided according to standard medical practice. Treatment with GSK2636771 will be withheld for any clinically significant GI toxicity.

Liver toxicity: In dogs, liver changes including minimal to mild single cell, perivascular hepatocellular necrosis, perivascular mixed inflammatory cell infiltrate, pigmented macrophages and Kupffer cells in the liver have been observed. Individual animals with liver changes had associated increased in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST). In the FTIH study (P3B115717), no serious (≥Grade 3) treatment-related elevations in liver function tests (e.g., AST, total bilirubin) have been observed. Eligibility criteria (see Section 4.1) will prevent any subject with significant liver dysfunction from enrolling on the study. Liver function laboratory tests will be measured frequently during therapy to monitor for potential toxicity and stopping criteria will be implemented, including dose reduction or discontinuation for clinically significant toxicity.

Rash: Events of Grade 1 or 2 rash (no grade ≥3) have been observed in 15% of subjects during the dose escalation phase in the FTIH study (P3B115717). Grade 3 rash was observed in 2 subjects in the ongoing expansion cohort of this study. Both improved with supportive care and interruption of study treatment. Both subjects restarted GSK2636771 at a lower dose. Medical history will be collected and physical exam will be conducted frequently during therapy to monitor for potential toxicity. Guidelines including dose modification and discontinuation (see Section 7.3.3) for the management of rash events are included in the protocol.

Cardiac effects: Increased heart weight and marked hypertrophy of the intramural coronary arteries characterized by thickening of the tunica intima and media was observed in one male dog. No microscopic evidence of myocardial damage was observed in this dog. However, reversible increases in mean arterial pressure, decreases in heart rate, and cardiac contractility that appeared to be secondary to elevation in blood pressure (BP) were observed in a single-dose safety pharmacology study in dogs 300 mg/kg. In the FTIH study (P3B115717), no serious (≥Grade 3) cardiac events have been observed. Subjects with a history of uncontrolled hypertension, heart failure, or known significant coronary artery disease will be excluded from studies of GSK2636771. Cardiac monitoring, including assessment of BP and heart rate, along with 12-lead electrocardiograms (ECGs) will be performed. Specific corrected QT interval (QTc) (see Section 7.2.1) and/or withdrawal criteria as well as guidance for the management of hypertension (see Section 7.3.2.1) are included in the protocol.

Hematopoietic effects: In dogs given 1000 mg/kg/day, lymphoid necrosis was observed in the spleen, lymph nodes, and gut associated lymphoid tissues with no associated changes in peripheral white blood cell (WBC) counts. Decreased thymus weights were observed in rats given 1000 mg/kg/day, with mildly increased mean total WBC, neutrophil, monocyte, and lymphocyte counts in female rats, likely due to GI and kidney inflammation. In the FTIH study (P3B115717), no Grade 3 treatment-related hematopoietic changes have been observed. Eligibility criteria (see Section 4.1) will exclude a subject with clinically significant, abnormal hematology laboratory parameters. Complete blood counts with differential will be monitored frequently to identify and assess hematologic toxicity. Supportive therapy will be provided according to local standard medical practice. Treatment with GSK2636771 will be withheld for a clinically significant toxicity.

Because of published non-clinical data indicating that p110β plays an important role in adenosine diphosphate (ADP)-induced platelet aggregation [Martin, 2010; Nylander, 2012], subjects with a history of congenital platelet function defects will not be eligible. In addition, concomitant usage of anti-platelet agents that act at platelet purinergic receptors is prohibited. Caution is recommended when GSK2636771 and aspirin are used concomitantly.

Reproductive effects: To reduce the risk of reproductive effects from GSK2636771 based upon a bursal hemorrhage noted in the ovary of 3 rats (two after 4 weeks dosing and one following a 2-week recovery period) given 1000 mg/kg/day, specific guidelines and precautions for male subjects (and their female partners of childbearing potential) are provided in the protocol (see Section 11.1).

1.4.1.2. Enzalutamide

Seizure. In the placebo-controlled Phase III clinical trial (AFFIRM) of subjects with mCRPC who had received docetaxel therapy, enzalutamide was administered at a dose of 160 mg daily (N = 800) versus placebo (N = 399). Seizure occurred in 0.9% of subjects receiving enzalutamide.

Caution should be used in administering enzalutamide to subjects with a history of seizures or other predisposing factors including, but not limited to, underlying brain injury, stroke, primary brain tumors or brain metastases, or alcoholism. In addition, the risk of seizure may be increased in subjects receiving concomitant medicinal products that lower the seizure threshold and therefore, subjects requiring such products should be excluded (Section 10.2). Enzalutamide should be discontinued if a seizure occurs while on treatment.

Cardiovascular effect. The AFFIRM study excluded subjects with recent myocardial infarction (within 6 months of study enrollment) or unstable angina (within 3 months of study enrollment), New York Heart Association (NYHA) Class III or IV heart failure (Appendix 2) except if left ventricular ejection fraction (LVEF) ≥45%, long QT, QT interval corrected by Fridericia's formula (QTcF) >470 msec, bradycardia or uncontrolled hypertension. Eligibility criteria will prevent any subject with significant cardiovascular disease from enrolling on the study.

1.4.1.3. Potential Overlapping Toxicities

Diarrhea: According to the prescribing information for enzalutamide, Grade 1 to 4 diarrhea was reported in 22% of subjects (N=800) with Grade 3 or 4 diarrhea reported among 1% of these subjects (versus 0.3% of placebo treated subjects). Diarrhea is an observed AE with GSK2636771 monotherapy (reported in 42% of subjects overall, regardless of causality; Grade 2 events in 6% of subjects and Grade 1 in all others; no Grade 3 or 4 events), diarrhea would be considered a potential overlapping event for GSK2636771 in combination with enzalutamide.

Fatigue: Based upon data reported for the integrated safety population for enzalutamide, fatigue was reported in 40.5% (422/1043) of subjects, resulting in 0.8% (8/1043) subjects from discontinuing treatment with enzalutamide. Fatigue may also be seen as an expected adverse effect due to androgen deficiency in this subject population. With GSK2636771 monotherapy, fatigue has been reported in 30% of subjects (N=53), mostly Grade 1 or 2 with 4% of subjects reporting Grade 3 or higher events. Given the potential of occurrence of fatigue from any of the study treatments, it is considered a potential overlapping event for the combination treatment of GSK2636771 with enzalutamide.

1.4.1.4. Risk of Drug-Drug Interaction

The risk for GSK2636771 to affect enzalutamide via enzymes of CYP3A4 and CYP2C8 is low but not fully discharged. It is unknown if enzalutamide could potentially affect the exposure of GSK2636771 via UDP-glucuronosyltransferase (UGT) inhibition or induction, while the drug-drug interaction (DDI) risk on GSK2636771 via organic

anionic transferase protein (OATP) transporter inhibition by enzalutamide is considered low due to high permeability of GSK2636771.

1.4.2. Benefit Assessment

This is the initial clinical experience with GSK2636771 in combination with enzalutamide, therefore, the benefit:risk has yet to be established. The benefit:risk should be favorable if the anticipated level of efficacy is demonstrated.

There is a risk of lack of efficacy with the combination as subjects entering the study will have progressed after receiving enzalutamide. Such a risk may be acceptable given the following:

- Further treatment with enzalutamide may continue to provide benefit as seen from the limited data suggesting some evidence of response in patients receiving abiraterone following abiraterone, enzalutamide following abiraterone, and from abiraterone following enzalutamide. Rate of growth may still be lower with enzalutamide than without enzalutamide (precedent from trastuzumab beyond progression). A 14-day run-in period of treatment with enzalutamide monotherapy will be continuous with prior enzalutamide therapy, with the exception of an allowed 30 day drug holiday from enzalutamide treatment, in order to achieve near-steady state enzalutamide exposure.
- Mechanisms of resistance to enzalutamide may provide less growth activity relative to unrestrained AR stimulation upon withdrawal of enzalutamide
- Mechanism of response may rely upon activation of the PI3K pathway and inhibition of the PI3K pathway while maintaining AR inhibition may be efficacious.

Additional considerations for subjects who participate in this study may include:

- Potential benefit of receiving GSK2636771 in combination with enzalutamide treatment during study duration that may have clinical utility
- Contribution to the process of developing a new treatment in mCRPC
- Medical evaluations/assessments associated with study procedures (e.g., physical examinations, ECGs, clinical laboratory tests, etc.)

1.4.3. Overall Benefit:Risk Conclusion

Taking into account the measures to be taken to minimize the risk to subjects participating in this study, the potential risks identified in association with GSK2636771 in combination with enzalutamide are justified by the anticipated benefits that may be afforded to subjects with mCRPC.

1.5. Rationale

1.5.1. Rationale for Study

Despite recent advances in the treatment of advanced prostate cancer, relapses are inevitable and mCRPC carries considerable morbidity along with shortened survival. Previous studies have indicated the importance of the PI3K pathway in prostate cancer. Therapeutic approaches that simultaneously inhibit both the AR and PI3K pathways may be more effective than inhibition of either pathway alone in mCRPC. Enzalutamide is an AR inhibitor indicated for the treatment of patients with mCRPC. This study is designed to investigate whether the PI3K pathway inhibitor can be co-administered safely with enzalutamide, thus allowing further investigation of their ability to reverse resistance to this AR inhibitor. Future studies may also assess whether the combination can delay the onset of resistance in enzalutamide-naïve CRPC or increase the response rate to enzalutamide.

1.5.2. Rationale for Study Population

A common event in prostate cancer progression is the loss of tumor suppressor PTEN in 40 to 50% of mCRPC patients that results in the activation of the PI3K pathway. Subjects with PTEN-deficient tumors are selected for this study as these tumors are more likely to have activation of the PI3K pathway and to potentially benefit from specific inhibition of this pathway. Tumors of subjects who have progressive disease following prior AR pathway inhibition with enzalutamide are likely to be reliant on resistance pathways, such as the PI3K pathway. In addition, these two pathways (PI3K and AR) are believed to modulate each other. Continued suppression of the AR pathway is a hallmark of treatment in mCRPC, and thus, this treatment approach is included in this study.

1.5.3. Dose Rationale

This study will be the first clinical experience with the combination of GSK2636771 + enzalutamide. Therefore this study will evaluate the safety of the combination regimen in order to determine its future development. Based on current clinical experience, overlapping toxicities, other than diarrhea and fatigue, are not anticipated with the combination. Subjects will be enrolled only if they are currently tolerating a full dose of enzalutamide. Enzalutamide will be administered at the approved dose of 160 mg once daily and should remain fixed during treatment.

Results from a study of inhibition of PI3Kβ in PC-3 human prostate tumors grown subcutaneously in female nude mice suggest that GSK2636771 concentrations must be above a target level to maintain inhibition of the target enzyme. After treatment with GSK2636771, inhibition of phosphorylated AKT (pAKT) occurred rapidly (within 1 hr) with the maximum inhibition (80%) occurring 2 hrs after administration of 10 mg/kg in the mice. Doses of 25 mg to 500 mg GSK2636771 have been investigated in Study P3B115717. The range of blood GSK2636771 trough concentrations (C24) at steady-state in the 200 mg once daily cohort of Study P3B115717 (2.62 – 13.4 μg/mL) exceeded the largest Cmax observed in mice after administration of 10 mg/kg/day (1.093 μg/mL). Therefore, preliminary PK results from Study P3B115717 demonstrate that doses of

200 mg or greater once daily achieved systemic exposure to GSK2636771 that resulted in pharmacologic effects consistent with inhibition of PI3Kβ in preclinical models.

Changes in phosphorylated and total protein levels of AKT, GSK3β and p70S6K in the platelet rich plasma (PRP) collected at various time points on Day 1 and Day 22 of treatment with GSK2636771 were quantified to assess the PI3K pathway inhibition. Of the 23 subjects treated with 25 to 500 mg GSK2636771, the data from pre- and post-dose on Day 1 revealed that 19 subjects had a >50% decrease in phospho (Ser473)/total AKT at 2 hrs. Thirteen of the 20 subjects treated with 100 to 500 mg GSK2636771 had >80% decrease in phospho (Ser473)/total AKT between pre-treatment and 1 to 10 hrs post-dose on Day 1. A similar decrease in phospho-GSK3β (Ser9), an AKT substrate, was also observed. These data suggest that treatment with GSK2636771 at the explored doses results in pathway inhibition (a surrogate to target engagement) in PRP.

A dose of 400 mg of GSK2636771 once daily was determined to be the MTD and was selected as the recommended Phase II dose (RP2D) for GSK2636771 monotherapy treatment based on safety, PK, and pharmacodynamic (PD) data from Study P3B115717. The proposed starting dose of GSK2636771 in the present study will be 300 mg once daily which is 75% of the RP2D as a single agent determined in Study P3B115717. The starting dose for the present study is lower than the monotherapy RP2D to decrease the probability of overlapping toxicities with GSK2636771 and enzalutamide. Preliminary results from Study P3B115717 indicate that 300 mg once daily of GSK2636771 will result in systemic exposure that resulted in effects consistent with pathway inhibition.

For enzalutamide, the approved dose of 160 mg once daily was selected. Given the long t1/2 of enzalutamide, a run-in period of 14 days is included in the study design. The intent of this run-in period is to achieve near-steady state plasma concentrations of enzalutamide prior to initiating combination therapy with GSK2636771.

1.5.4. Endpoint Rationale

This study has been designed to fully explore the safety of the combination as this represents the first clinical experience for the combination. The dose-finding cohorts are large enough that less common but important safety risks may be identified. Any clinical efficacy seen will also be described as the population under study has great unmet need for active therapies, and will be assessed through the use of response criteria defined in the Prostate Cancer Working Group 2 (PCWG2) guidelines.

In the dose expansion phase, the cohorts are large enough to analyze the 12-week non-progressive disease (PD) rate.

2. OBJECTIVES AND ENDPOINTS

2.1. Hypothesis

Primary Hypothesis: The addition of a targeted PI3K pathway inhibitor (GSK2636771) to enzalutamide can be safely administered with ongoing enzalutamide treatment.

Secondary Hypothesis: The addition of a targeted PI3K pathway inhibitor (GSK2636771) to enzalutamide can limit mCPRC progression in a clinically meaningful way for at least 12 weeks. The null hypothesis is that the 12-week non-PD rate is not attractive (≤5%). The alternative hypothesis is that the rate is clinically meaningful and, therefore, the compound warrants further development (≥30%). This hypothesis will be tested using a combination of data provided in both the dose escalation and dose expansion phases.

2.2. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of GSK2636771 + enzalutamide administered orally once daily continuously in subjects with mCRPC.	• AEs, SAEs, DLTs, and changes in laboratory values, ECGs, and vital signs (BP, temperature and heart rate)
• To determine the RP2D of orally administered GSK2636771 + enzalutamide in subjects with mCRPC.	• Safety and tolerability as assessed by AEs, SAEs, DLTs, and changes in laboratory values, ECGs, and vital signs (BP, temperature and heart rate)
• To evaluate lack of progression in the dose expansion subjects with mCPRC by rate of subjects who do not progress for 12 weeks	• Non-PD rate for 12 weeks according to PCWG2 criteria (either by RECIST 1.1, or progression in bone or PSA progression with accompanying progression by RECIST 1.1 or bone scan when baseline radiological or bone disease present or PSA progression if no other baseline disease).
Secondary	
• To evaluate the clinical activity of oral GSK2636771 + enzalutamide in the treatment of mCRPC (PTEN deficient)	• PSA50 response rate defined as the percent of subjects achieving PSA50 at 12 weeks or thereafter (PSA50 is ≥50% decrease in PSA from baseline) • Objective Response Rate (ORR) defined as complete response (CR) rate plus partial response (PR) rate per RECIST 1.1 • Time to PSA progression according to PCWG2 criteria • Time to radiological progression according to PCWG2 criteria (either by RECIST 1.1, PSA progression and/or progression in bone) • Radiological progression free survival (rPFS) per RECIST1.1 and/or bone scans

Objectives	Endpoints
• To determine the effect of GSK2636771 on enzalutamide PK following repeat-dose oral administration.	• Plasma concentrations of enzalutamide and N-desmethyl enzalutamide.
• To determine the PK of GSK2636771 in the presence of enzalutamide.	• Blood GSK2636771 concentrations.
Exploratory	
• To determine the frequency of PTEN deficiency in subjects with mCRPC	• Frequency of PTEN-deficient mCRPC reported in subjects based on pre-screened tumors
• To determine the mechanism of PTEN deficiency	• PTEN deletion, mutation or promoter methylation
• To identify additional biomarkers (DNA, RNA or protein based) in tumor or in circulation that may predict response to oral GSK2636771 + enzalutamide	• Response prediction biomarkers based on analysis of DNA, RNA, and proteins from surrogate tissues (e.g., cfDNA) and/or tumor tissue
• To determine the effect of enzalutamide with GSK2636771 on the kinetics of tumor growth	• Longitudinal tumor size measurements; serum PSA levels, change from baseline in CTCs
• Evaluation of biomarkers in CTCs that may predict response to combination	• AR expression, PTEN FISH and other genomic evaluations in CTCs
• Evaluation of tumor tissue to explore explanation for the mechanism of resistance to combination therapy	• Based on analysis of DNA, RNA and proteins from tumor tissue obtained at time of progression after initially responding to combination therapy
• To determine pharmacodynamic effects of drug treatment	• RNA/protein analysis of pre/post treatment tumor biopsies

Abbreviations: AEs, adverse events; AR, androgen receptor; BP, blood pressure; cfDNA, circulating-free deoxyribonucleic acid; CTC, circulating tumor cells; DLTs, dose limiting toxicities; DNA, deoxyribonucleic acid; ECG, electrocardiogram; FISH, fluorescent in situ hybridization; mCRPC, metastatic castration-resistant prostate cancer; PCWG2, Prostate Cancer Working Group 2; PD, progressive disease; PK, pharmacokinetics; PSA, prostate-specific antigen; PTEN, phosphatase and tensin homolog; RECIST, Response Evaluation in Solid Tumors; RNA, ribonucleic acid; RP2D, recommended Phase II dose; SAE, serious adverse event(s)

3. INVESTIGATIONAL PLAN

This is a Phase I, open-label, non-controlled, non-randomized dose finding, dose escalation, multicenter study to determine the RP2D of the oral PI3Kβ inhibitor, GSK2636771 in combination with enzalutamide in subjects with mCRPC. The study will be conducted in two phases: the Dose Escalation Phase and the Dose Expansion Phase. Each phase of the study will consist of a pre-screening period, a screening period,

three treatment periods (Enzalutamide Run-In Period, Combination Treatment Period and Treatment Continuation Period), and a post-treatment follow-up visit.

Subjects with PTEN deficient mCRPC (determined during pre-screening), who have documented progression per Prostate Cancer Working Group 2 (PCWG2) criteria (either by Response Evaluation Criteria in Solid Tumors [RECIST] 1.1, prostate-specific antigen [PSA] progression, and/or progression in bone), will be enrolled in the Dose Escalation Phase and Dose Expansion Phase of the study.

In the Dose Escalation Phase, subjects will be enrolled into dose-finding cohorts to evaluate the safety and PK to guide the selection of the MTD of GSK2636771. Dosing decisions will be based on all available data at the end of each DLT reporting period (the first 28 days of combination treatment). Decisions for dose determination for subsequent cohorts will be documented and maintained by each site and in the GSK Trial Master Files (TMF).

In the Dose Expansion Phase, subjects will be assigned to receive GSK2636771 at doses identified at or below the MTD in the Dose Escalation Phase while continuing treatment with enzalutamide to evaluate the long-term safety of the combination as well as the 12-week non-PD rate. This may include multiple dose levels in order to establish the RP2D of the combination treatment at the conclusion of combination treatment in any dose level.

Safety Assessments: Throughout the study, safety will be assessed through standard measures, including physical examinations, vital signs, clinical laboratory tests, 12-lead ECGs and monitoring of AEs. Efficacy will be assessed by physical examination, computed tomography (CT) scan or magnetic resonance imaging (MRI), radionuclide bone scans, circulating tumor cells (CTC) enumeration, and PSA. Pharmacokinetic (PK) blood samples will be collected from all subjects to evaluate if there is an effect of GSK2636771 on the PK of enzalutamide and to quantify the systemic exposure to GSK2636771.

Clinical Response Assessments: The determination of clinical response, including disease progression, will be assessed by-the PCWG2 criteria (see Section 8.8.2). The assessment of the 12 week non-PD-rate will also be determined by PCWG2 criteria (either by RECIST 1.1, PSA progression, and/or progression in bone).

Biomarker Assessments: Planned biomarker assessments include: 1) Identify potential predictive biomarkers (protein, DNA, ribonucleic acid [RNA] based) in archived tumor tissue/pre-treatment biopsies; 2) enumeration of CTCs in circulation and evaluation of genetic alterations or expression of AR, PTEN or other genes in isolated CTCs; 3) Assessment of circulating DNA/RNA and other soluble markers in plasma to better understand clonal evolution and other predictive circulating biomarkers; and 4) understand the mechanism of resistance in tumor tissues biopsies (optional) at time of progression 5) assess pharmacodynamic effects by collecting pre/post treatment tumor biopsies

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Tables (Section 8.1) are essential.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Reference Manual (SRM). The SRM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

3.1. Pre-Screening and Screening

All subjects will be required to undergo pre-screening to determine the PTEN deficiency status of their tumor at the GSK selected laboratory.

- Pre-screening may be performed prior to confirmation of progression on enzalutamide
- Subjects will be required to sign a separate Pre-Screening Informed Consent Form (ICF) to allow for pre-screening of archived or fresh tumor biopsy samples
- Details of the PTEN requirements are provided in SRM.

Only subjects who have completed pre-screening and who have been confirmed to have PTEN-deficient tumor will be eligible to enter into screening. Subjects will be required to sign another Informed Consent Form (ICF) for the main study at Screening prior to initiation of any screening procedures or assessments.

Screening assessments will be conducted to determine subject eligibility for enrollment into the study. Enrollment is defined as the first dose of enzalutamide monotherapy on Day 1 of the Enzalutamide Run-In Period. The screening assessments should be completed within 14 days of the planned first dose of enzalutamide in the Enzalutamide Run-In Period, but may be shorter if all entry criteria have been evaluated and met.

3.2. Treatment Periods

3.2.1. Enzalutamide Run-In Period

Subjects will be enrolled in the 14-day run-in period and receive enzalutamide monotherapy at the approved dose of 160 mg once daily. The intent of the Run-in period is to achieve near-steady-state plasma concentrations of enzalutamide prior to initiating combination therapy with GSK2636771.

Subjects who experience an intolerable toxicity causing a dose interruption or dose reduction during the Enzalutamide Run-In Period will require approval from the GSK Medical Monitor in order to continue in the study. Those subjects not eligible for treatment in the Combination Treatment Period will not be considered in the evaluation of DLTs and may be replaced.

Subjects who discontinue the study during the Enzalutamide Run-In Period will be asked to complete the post-treatment follow-up visit within 30 days of the last dose of enzalutamide.

3.2.2. Combination Treatment Period

Subjects who complete the Enzalutamide Run-In Period will begin oral GSK2636771 treatment on Week 1, Day 1 of the Combination Treatment Period while continuing to receive enzalutamide to evaluate safety of the combination therapy.

3.2.3. Treatment Continuation Period

Subjects will continue to receive the combination treatment of GSK2636771 + enzalutamide from Week 5 and thereafter will be seen in the clinic every 4 weeks. Subjects will continue study treatment until clinical benefit is no longer apparent (see Section 5.2), in the opinion of the treating physician, or until unacceptable AE, withdrawal of consent, permanent discontinuation of treatment or death.

The study will be considered completed approximately 6 months after the last subject begins study treatment. However, based on emerging data, the study may continue to collect further efficacy data if warranted.

3.2.4. Post-Treatment Follow up

A post-treatment follow-up visit will be performed within 30 days of the last dose of study treatment(s) for all subject who permanently discontinue study treatments, during the Enzalutamide Run-In Period (and/or do not enter the Combination Treatment Period), or for those who permanently discontinue study treatments during the Combination Treatment or Treatment Continuation Period due to disease progression.

Subjects who withdraw from the study during the Combination Treatment or Treatment Continuation Period ***without*** disease progression should complete the Extended Follow-up Visits where they will be contacted every 3 months (±14 days) until disease progression, death, withdrawal of consent, or subject is lost to follow-up. Contact may include a clinic visit, a telephone contact, or an e-mail. The initiation of any new anti-cancer treatments and date of last contact should be documented. Subjects who discontinue the Extended Follow-Up Visits for reasons **other than** death, loss to follow-up, or withdrawal of consent should have a Post-Extended Follow-Up/EOS Visit performed.

3.3. Discussion of Study Design

This is the first clinical experience with the combination of GSK2636771 with enzalutamide. The study is designed to provide a robust evaluation of the safety for the combination treatment. Additional doses and/or dosing schedules of GSK2636771 with enzalutamide may be explored in each of the cohorts, if necessary.

The dosing of enzalutamide will be administered at the US FDA approved dose (refer to the Prescribing Information for enzalutamide [Xtandi, 2016]. Study treatment will continue until there is no longer clinical benefit (see Section 5.2), in the opinion of the investigator, or until an unacceptable AE (including stopping criteria outlined in Section 7.2), withdrawal of consent, permanent discontinuation of study treatment, or death

occurs. Investigators will use the PCWG2 criteria to determine clinical response to each treatment.

3.4. Dose Escalation Phase

In the Dose Escalation Phase, the dose of GSK2636771 will follow a modified 3+3 dose escalation procedure to evaluate the safety and PK for each combination dose level and to guide selection of the combination dose for dose expansion.

A minimum of 3 subjects may be enrolled in each subsequent cohort until the MTD (see Section 3.4.4) is defined. Evaluation of at least 3 subjects who have completed 28 days of treatment with the combination is required prior to dose escalation to the next cohort. Dose escalation decisions will be by the investigator(s), GSK Medical Monitor, pharmacokineticist, and statistician following review of all available data. Dose escalation will proceed with the increment of dose increase or decrease as determined by toxicity rules outlined in Table 1.

Table 1 3+3 Dose Escalation Guidelines Based on Toxicity

Number of Subjects with a DLT	Action
0 out of 3 subjects	Escalate to next dose level.
1 out of 3 subjects	Accrue 3 additional subjects at current dose level for a total of 6 subjects
1 out of 6 subjects	Escalate to the next dose level.
2 or more subjects in a dosing cohort (up to 6 subjects)	Dose-escalation will be stopped. At this dose level, the MTD has been exceeded (highest dose administered). Either evaluate at a lower intermediate dose (3+3 dosing) or expand a prior cohort up to approximately 20 subjects per treatment arm.

Abbreviations: DLT, dose limiting toxicity; MTD, maximum tolerated dose

If the combination doses in Cohort 1 are not tolerable, lower doses will be evaluated. If the de-escalation cohort (Cohort -1) is not tolerable, additional dose levels of GSK2636771 or alternative dosing schedules may be explored based upon ongoing assessment of safety, PD and PK. Dose modification decisions will be made utilizing all available data at the end of each DLT reporting period (the first 28 days of combination treatment).

Dose escalation will proceed until the MTD of the combination regimen is identified. If the dose(s) administered to a given cohort exceeds the MTD as defined in Section 3.4.4, intermediate doses may be explored. Dose escalation decisions will take into account all available data, including the safety profile and PK data of prior cohorts throughout the time subjects are on study, which will be reviewed by the investigator(s), GSK Medical Monitor, pharmacokineticist and statistician. The dose escalation decision for the subsequent cohort and rationale will be documented in writing with copies maintained in the site's study files and the TMF at GSK. In the absence of DLTs, the dose of GSK2636771 may be escalated to the MTD of 400 mg as determined in the FTIH study (P3K115717).

If diarrhea (in the absence of aggressive diarrhea management), fatigue, or rash defines the MTD, the cohort in which the toxicity is observed may be expanded by at least 3 subjects and the efficacy of supportive care evaluated prior to further dose escalation. If supportive care measures ameliorate the toxicity without recurrence of the toxicity, further dose escalation may be conducted in the presence of appropriate supportive care.

Table 2 Dose Escalation Cohorts

Cohort	N	GSK2636771	Enzalutamide
-1	3 - 6	200 mg once daily	160 mg once daily
1	3 - 6	300 mg once daily	160 mg once daily
2	3 - 6	400 mg once daily	160 mg once daily

3.4.1. Cohort Expansion

Any cohort may be expanded up to 12 subjects in order to collect adequate data on safety, PD or PK. Subjects may be enrolled at previously completed dose levels for the purpose of obtaining additional PK and/or PD data.

3.4.2. Alternative Dosing Schedules

Alternative schedules may be evaluated if emerging data suggest that continuous daily dosing will result in excessive toxicity. Only those alternative schedules exploring dosing less frequent than current dosing schedule will be evaluated. If alternative dosing schedules are explored, PK sampling times will be modified to reflect the new dosing schedule.

3.4.3. Definition of Dose Limiting Toxicity

The DLT criteria apply only during the Dose Escalation Phase, and impacts the decisions around whether the MTD has been determined, and/or decisions around whether to escalate or de-escalate the next dose level, but do not apply to the mandated management of an individual subject as with the liver stopping criteria.

Subjects who fail to receive at least 75% of the protocol-specified study treatment during the DLT reporting period (the first 28 days of combination treatment) for reasons OTHER than toxicity will be replaced if data from the replacement subject could impact the dose selection criteria.

An event will be considered a DLT if the event is attributed (definitely, probably or possibly) to study treatment, occurs within the first 28 days of combination treatment (DLT reporting period), and meets one of the following criteria:

- Grade 3 or greater non-hematologic toxicity that cannot be controlled with routine supportive measures (e.g., antiemetics, antidiarrheals)
- Grade 4 neutropenia lasting >5 days

- Febrile neutropenia, of any grade or duration as defined by Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0)

- Grade 4 thrombocytopenia

- Alanine aminotransferase (ALT) >3 times upper limit of normal (ULN) with bilirubin >2 times ULN or ALT ≥3 times ULN and ≥1.5 times baseline ALT value, if enrolled with liver metastases/tumor infiltration at baseline), together with bilirubin ≥2 times ULN)

Any Grade 2 or greater toxicity (per CTCAE v4.0) that occurs beyond the 28-day DLT reporting period which in the judgment of the investigator and GSK Medical Monitor would be considered dose limiting will also be considered a DLT.

Subjects who experience an intolerable toxicity causing a dose interruption or dose reduction during the Enzalutamide Run-In Period (before the start of GSK2636771 combination treatment) will require approval from the GSK Medical Monitor in order to continue in the study. Those subjects not eligible for the combination phase will not be considered in the evaluation of DLTs and may be replaced.

3.4.4. Maximum Tolerated Dose

The MTD is defined as the highest dose at which no more than one of 6 subjects experience a DLT during the first 28 days of combination therapy. The MTD will be exceeded if 2 or more subjects in a cohort of up to 6 subjects experience a DLT.

3.5. Dose Expansion Phase

Enrollment in the Dose Expansion Phase of the study may begin once a suspected MTD has been determined in the Dose Escalation Phase. Up to 20 additional subjects per dose level may be enrolled to better characterize the safety profile, PK, and clinical activity of the recommended doses of the combination of GSK2636771 + enzalutamide for future studies. One or more combination doses may be explored in the Dose Expansion Phase based on the MTD identified in the Dose Escalation Phase of the study. To fully evaluate additional combination doses, up to 20 additional subjects per dose level may be enrolled.

In the Dose Expansion Phase, final analyses will occur 6 months after the last subject is enrolled to allow for adequate collection of safety information. Those subjects that have not completed the treatment phase of the study (see Section 5.2) at the time of the final analysis may be transferred to a continued access study, if available.

3.6. Recommended Phase II Dose

The RP2D will be considered the lowest dose of GSK2636771 explored (at or below MTD) that provides adequate PK exposure and biologic activity with a superior tolerability profile. If multiple dose levels are explored in dose expansion, the RP2D will be based on the totality of data.

3.7. Intra-subject Dose Escalation

Subjects enrolled in a lower combination cohort may be subsequently escalated to a higher dose combination once safety has been established and after consultation with the GSK Medical Monitor.

3.7.1. Evaluation of Futility

Futility will be evaluated when there is adequate enrollment. The methodology for evaluation of futility is based on the predictive probability of success if enrollment continues to 20 subjects per dose level [Lee, 2008]. The predictive probability design is similar to a Green-Dahlberg design in that it allows for early stopping for futility. The differences are that the predictive probability design allows for evaluation of stopping rules after each subject, rather than at only two stages, once a minimum number of subjects are evaluable. In this particular study, we will stop only for futility. While the two designs have similar type I and type II error rates, the probability of early termination is greater with the predictive probability design.

After 10 subjects have been enrolled to examine safety and 12-week non-PD rate, the number of subjects who have not progressed in 12 weeks will guide further enrollment according to the rules summarized in Table 3. The decision to terminate the Dose Expansion Phase will not depend solely on the results of the statistical methodology, but will take all factors into account. These factors include the representation of predictive biomarkers, such as Androgen receptors, in the subjects treated at the time of interim analysis; and the totality of the safety, tolerability, PK, and PD data. Additional subjects targeting a specific biomarker profile may be enrolled in the cohort at the discretion of the study team, even if the predictive probability suggests a low likelihood of clinical activity in this cohort.

Table 3 Stopping Rules for Predictive Probability Design

Number of Subjects Enrolled	≤ This Number of Responses[1] to Stop Early for Futility
10	0
11	0
12	0
13	0
14	0
15	0
16	1
17	1
18	1
19	1
20	2

Abbreviations: PCWG2, Prostate Cancer Working Group 2; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors

1. Response for the purpose of futility is defined as lack of disease progression at 12 weeks according to PCWG2 criteria. PSA

progression in subjects with baseline radiological or bone disease will require RECIST or bone progression in addition to PSA progression to be determined a disease progressor.

3.8. Continued Treatment

A subject may continue study treatment until the treatment discontinuation criteria are met (see Section 5.2). Additional guidelines regarding dose modifications are provided in Section 7.1.

3.9. Treatment Assignment

Each subject will be assigned a unique subject number that will remain consistent for the duration of the study. This number will be assigned sequentially from a range of subject numbers provided for each site in the SRM. Upon completion of all required pre-screening and screening procedures and assessments, eligible subjects must be approved for enrollment by a member of the GSK central study team according to the procedures detailed in the SRM.

3.10. Blinding

This is an open-labeled study.

4. STUDY POPULATION

4.1. Subject Selection Criteria

4.1.1. Number of Subjects

A total of between approximately 44 and 64 subjects will be enrolled in this study**.**

Dose Escalation Phase: The number of dose levels and the level at which the MTD is reached cannot be determined in advance. An adequate number of subjects will be enrolled to establish the recommended dose for further study. It is estimated that approximately 24 subjects will be enrolled in the Dose Escalation Phase.

Dose Expansion Phase: In the Dose Expansion Phase, it is estimated that approximately 20 subjects will be enrolled, with evaluation for futility after the first 10 subjects have completed 12 weeks of treatment (see Section 3.7.1). This analysis may occur using the combination of the dose escalation and dose expansion population. If multiple dose levels of GSK2636771 are examined during dose expansion to establish the RP2D, each dose level cohort will enrol approximately 20 subjects, increasing the overall number of subjects targeted for enrolment in this study.

4.1.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on GSK2636771 or enzalutamide that may impact subject eligibility is provided in the IB for GSK2636771 [GlaxoSmithKline Document Number 2011N117133_01] and the Prescribing Information for enzalutamide [Xtandi, 2016].

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

To be eligible for this study, subjects must meet ALL of the following criteria:

1. Signed written informed consent provided

   NOTE: Separate ICFs must be signed prior to the pre-screening and screening procedures.

2. Males ≥18 years of age (at the time written consent is obtained for pre-screening)
3. Histologically or cytologically confirmed diagnosis of prostate adenocarcinoma, surgically castrated or continuous medical castration (for ≥8 weeks prior to Screening)
4. Serum testosterone <50 ng/dL (1.7 nM/L)
5. PTEN-deficient tumor as documented from archived or fresh (from pre-treatment biopsy) tumor tissue analyzed by a GSK selected laboratory
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
7. Has completed at least 12 weeks of prior continuous therapy with enzalutamide
8. Has not been without enzalutamide treatment for >30 days prior to enrollment
9. Has documented disease progression following treatment with enzalutamide at time of Screening

   NOTE: Disease progression is defined by one or more of the following criteria:

   - PSA progression defined by PCWG2 criteria (see Section 8.8.2.1), or
   - Soft tissue disease progression defined by RECIST 1.1 (see Appendix 4), or
   - Bone disease progression defined by PCWG2 criteria (see Section 8.8.2.2)

10. Able to swallow and retain orally administered medication.
11. Adequate baseline organ function at time of Screening defined as:

Hematologic	
ANC Hemoglobin Platelets PT/INR and PTT	≥1.5 x 10^9/L ≥9 g/dL ≥100 x 10^9/L ≤1.3 x ULN
Hepatic	
Albumin Total bilirubin[1]	≥2.5 g/dL ≤1.5 x ULN
AST ALT[1]	≤2.5 x ULN ≤2.5 x ULN or >2.5 x ULN but ≤5 x ULN with documented liver metastases or tumor infiltration

Renal	
Urine Protein (via dipstick)[2] UPC[3,4] Serum Creatinine **OR** Estimated Serum Creatinine Clearance[5] **OR** 24-hr Urine Creatinine Clearance	0/+1 <0.2 ≤ULN ≥60 mL/min ≥60 mL/min
Cardiac	
LVEF	≥50% by ECHO or MUGA
Other	
Serum Phosphate Serum Calcium[6] (corrected) Ionized Calcium[6] Vitamin D[6]: 25-OH D and 1,25-OH2 D	WNL WNL WNL WNL

Abbreviations: ANC, absolute neutrophils count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; ECHO, echocardiogram; INR, international normalization ratio; LLN, lower limit of normal; LVEF, left ventricular ejection fraction; MUGA, multigated acquisition scan; PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; UPC, urine protein to creatinine ratio; WNL, within normal limits

1. If ALT or bilirubin values are outside range listed due to Gilbert's syndrome or asymptomatic gallstones, subject remains eligible.
2. If subject's urine protein is >1+ (via dipstick), then UPC ratio will be calculated. Subject will be considered eligible for study if UPC ratio is <0.2.
3. UPC ratio is only to be calculated if subject's urine protein is >1+ via dipstick.
4. The UPC value will not be used to determine eligibility for subjects who are unable to obtain uncontaminated urine samples due to their disease.
5. Estimated by the CKD-EPI equation (see Appendix 3).
6. Vitamin D supplementation may be added to achieve values WNL. Calcium supplements should be added for subjects with calcium values near the lower normal limit.

NOTE: Laboratory results obtained during Screening should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the investigator may opt to retest the subject and the subsequent within range screening result may be used to confirm eligibility.

12. Male subject with a female partner of childbearing potential or pregnant must agree to use two acceptable methods of contraception from time of Screening until 3 months after the last dose of study treatments (see Section 11.1).

4.1.3. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting ANY of the following criteria must not be enrolled in the study:

1. Prior treatment with:

- Anti-cancer therapy (e.g., chemotherapy with delayed toxicity, immunotherapy, biologic therapy or chemoradiation) within 21 days (or within 42 days if prior nitrosourea or mitomycin C containing therapy) prior to enrollment and/or daily or weekly chemotherapy with the potential for delayed toxicity within 14 days prior to enrollment

  Exception: Subjects may remain on luteinizing hormone releasing hormone (LHRH) agonists (i.e., leuprolide, goserelin, triptorelin or histrelin) and AR antagonists (e.g., bicalutamide, flutamide, nilutamide), except abiraterone.

  Exception: Subjects must have received prior treatment with enzalutamide.

- Any PI3K, AKT or mammalian target of rapamycin (mTOR) inhibitors
- Investigational drug(s) (other than enzalutamide) within 30 days or 5 half-lives, whichever is longer, prior to enrollment

2. Prior malignancy other than CRPC.

   Exception: Subjects who have been disease-free for 5 years, or subjects with a history of completely resected non-melanoma skin cancer or successfully treated *in situ* carcinoma are eligible.

3. Current use of or anticipated requirement during the study of any prohibited medication(s) (see Section 10.2)
4. Any unresolved ≥Grade 2 toxicity (per CTCAE 4.0) from previous anti-cancer therapy at time of enrollment, except alopecia or Grade 2 anemia (if hemoglobin is >9.0 g/dL)
5. Presence of any clinically significant GI abnormality or other condition(s) that may alter absorption such as malabsorption syndrome or major resection of the stomach or substantial portion of the small intestine

   NOTE: If clarification is needed as to whether a GI abnormality, condition or resection will significantly affect the absorption of study treatment, contact the GSK Medical Monitor.

6. Active peptic ulcer disease or history of abdominal fistula, GI perforation, or intra-abdominal abscess within 28 days prior to enrollment
7. Previous major surgery within 28 days prior to enrollment
8. Known active infection requiring intravenous (IV) or oral anti-infective treatment
9. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at time of Screening or within 3 months prior to enrollment
10. A positive pre-study drug/alcohol screening (testing at time of Screening is not required).
11. A positive test for human immunodeficiency virus (HIV) antibody (testing at time of Screening is not required).
12. Evidence of severe or uncontrolled systemic diseases (e.g., unstable or uncompensated respiratory, hepatic, renal or cardiac disease)

13. History of seizure or any condition that may predispose subject to seizure (e.g., prior cortical stroke or significant brain trauma).
14. History of loss of consciousness or transient ischemic attack within 12 months prior to enrollment
15. Has a QTc >450 msec or QTc >480 msec for subjects with bundle branch block (BBB)

    NOTES: The QTc is the QT interval corrected for heart rate by Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read.

    The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial.

    For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).
16. History or evidence of cardiovascular risk including any of the following:
    - Clinically significant ECG abnormalities including second degree (Type II) or third degree atrioventricular block
    - History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, stenting, or bypass grafting within the past 6 months prior to enrollment
    - Class III or IV heart failure as defined by the NYHA functional classification system (Appendix 2)
    - Left ventricular ejection fraction (LVEF) below 50%
    - Known cardiac metastases
17. Poorly controlled hypertension (defined as systolic blood pressure [SBP] of ≥150 mmHg or diastolic blood pressure [DBP] of >100 mmHg based on a mean of three measurements at approximately 2-minute intervals)

    NOTE: Initiation or adjustment of antihypertensive medication(s) is permitted if done 30 or more days prior to enrollment.
18. History of congenital platelet function defect (e.g., Bernard-Soulier syndrome, Chediak-Higashi syndrome, Glanzmann thrombasthenia, storage pool defect)
19. Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GSK2636771or enzalutamide or excipients.
20. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures.

21. Exposure to more than 4 investigational medicinal products (IMPs) within 12 months prior to enrollment

5. COMPLETION OR WITHDRAWAL OF SUBJECTS

5.1. Screen Failures

A subject will be considered a screen failure if:

- subject signs the pre-screening ICF but does not complete pre-screening, ***or***
- subject completes the pre-screening, signs the screening ICF but does not complete screening or does not meet the eligibility criteria for enrollment, ***or***
- subject is withdrawn from the study before receiving any study treatment

Minimal core data for screen failures will be collected from source documentation at the site, entered into the electronic case report forms (eCRFs), and transmitted to GSK. The minimal core data includes the following:

- Reason(s) for screen failure
- Demography
- Eligibility
- SAE (if applicable)

5.2. Permanent Discontinuation of Study Treatment(s)

Study treatment(s) will be permanently discontinued for any of the following reasons:

- Disease progression defined with regards to termination of study treatment as: Radiographic progression in soft tissue or bone by RECIST 1.1 for subjects with measurable disease, OR
- Bone progression on bone scan according to the PCWG2 criteria (Section 8.8.2.2), OR
- When it is determined in the opinion of the treating physician in collaboration with the subject that the subject is no longer clinically benefitting (NLCB) from treatment.

  NOTE: Subjects who are tolerating therapy and meet criteria for disease progression solely on the basis of rising PSA or for the worsening of an isolated disease site that is not clinically significant will NOT be required to discontinue treatment and can continue treatment until they are NLCB from treatment [Scher, 2016].

  NOTE: Subjects must meet the PCWG2 guidelines for disease progression to avoid premature discontinuation of study treatment(s).

- Unacceptable toxicity (including meeting liver chemistry stopping criteria as defined in Section 7.2)

NOTE: If the subject voluntarily discontinues from treatment due to toxicity, 'adverse event' will be recorded as the primary reason for permanently discontinuation on the eCRF.

- Substantial protocol deviation(s)
- Death
- Investigator's discretion
- Lost to follow-up
- Intercurrent illness that prevents further administration of study treatment(s)
- Withdrawal of consent by subject or proxy for further treatment and/or data collection
    - If subject withdraws consent for further treatment, the subject should return for Post-Treatment Follow-up Visit as indicated in the Time and Events Tables (Section 8.1).
    - If subject withdraws consent for further treatment and data collection, then no additional study visits, including a post-treatment follow-up visit, or data collection should occur. All samples collected for the biomarker analysis at the time of withdrawal will proceed for analysis to meet the intended objectives defined in this protocol, unless consent for further analyses is withdrawn by the subject.
- Study closure or termination

If study treatment(s) is/are permanently discontinued, the subject will not be allowed to be retreated. The primary reason for permanently discontinuing study treatment(s) must be documented in the subject's medical records and eCRF.

All subjects who have study treatment(s) permanently discontinued will have safety assessments at the time of discontinuation and during post-study treatment follow-up as specified in Time and Events Tables (Section 8.1).

Treatment Discontinuation without Disease Progression: All subjects who permanently discontinue study treatment(s) without disease progression should be followed for progression according to the protocol schedule until:

- A new anti-cancer therapy is initiated, or
- Disease progression occurs, or
- Death

5.3. Subject Completion

A subject will be considered to have completed the study if the subject dies or otherwise progresses during the study treatment or post-treatment follow-up period. All other subjects will be considered to have withdrawn from the study.

5.4. Study Completion

The study will be considered completed, having met the study objectives, approximately 6 months after the last subject begins study treatment. However, based on emerging data, the study may continue to collect further efficacy data if warranted. Per the European Union Clinical Trial Directive, the end of the study is defined as the last subject's last visit.

5.5. Treatment after the End of the Study

The investigator is responsible for ensuring that consideration has been given for the post-study care of the subject's medical condition whether or not GSK is providing specific post-study treatment. For this study, post-study treatment will not be provided.

Upon discontinuation from the assigned study treatment, subject should complete the required withdrawal and follow-up evaluations prior to transitioning to a rollover study if one is available, initiating further anti-cancer therapy or treatment with any investigational agent.

Refer to the Time and Events Tables (Section 8.1) for follow-up assessments and procedures.

6. INVESTIGATIONAL PRODUCT

The term 'study treatment' is used throughout the protocol to describe any combination of investigational products (IP) received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

A description of each IP is provided in the following sections.

6.1. GSK2636771 GSK Investigational Product

GSK2636771 will be provided to sites by GSK.

The contents of the label will be in accordance with all applicable regulatory and/or legal requirements.

Product name:	**GSK2636771**
Formulation description:	Each 100 mg capsule contains GSK2636771B (tromethamine, tris salt) equivalent to 100 mg of GSK2636771A **Shell composition:** gelatin, red iron oxide (E172) and titanium dioxide (E171)
Dosage form:	Capsule (gelatin)
Unit dose strength(s):	100 mg
Physical description:	100 mg: Pink, size 0 hard gelatin capsule
Route/Frequency/Duration:	Oral/once daily/continuous until treatment withdrawal
Dosing Instructions:	See Section 6.3.1 for dosing instructions.

6.2. Enzalutamide Non-GSK Product

Initially, in countries where it is approved (i.e., US), sites will need to obtain enzalutamide (Xtandi) from local commercial stock in order to provide enrolled subjects with an adequate supply of enzalutamide while on study.

In countries where regulatory authorities mandate that the Sponsor must supply all study treatment(s) required for study participation, GSK will provide an adequate supply of enzalutamide (from commercial stock) directly to the site for enrolled subjects.

Enzalutamide will be provided to subjects at no cost to begin taking enzalutamide on the first day (Day 1) of the Enzalutamide Run-In Period and throughout their participation in the study. If a subject does not qualify for entry into the study based on the tests or assessments performed during pre-screening and screening, then enzalutamide will not be provided to them.

The sourcing of enzalutamide from commercial stock will continue until which time (estimate within the first quarter of 2015) GSK will begin supplying all sites with an adequate inventory of commercial US sourced enzalutamide; an appropriate amendment will be made to the Quality section of the Investigational New Drug (IND) and Clinical Trials Application (CTA).

The contents of the label will be in accordance with all applicable regulatory requirements.

Product name:	**Enzalutamide (Xtandi)**
Formulation description:	Each capsule contains fill solution: enzalutamide, caprylocaproyl macrogolglycerides, butylhydroxyanisole, and butylhydroxytoluene
Dosage form:	Capsule (soft gelatin)
Unit dose strength(s):	40 mg
Physical description:	White to off-white oblong liquid filled soft gelatin capsule imprinted in black ink with ENZ
Route/Administration/ Duration:	Oral/once daily, within 5 minutes of GSK2636771 administration/ continuous until treatment withdrawal
Dosing Instructions:	See Section 6.3.2 for dosing instructions.

6.3. Administration of Study Treatments

Dosing Time: Subjects will be instructed to take their doses of study treatment (GSK2636771 and enzalutamide) at the same time each day if possible (24 hr intervals). Morning dosing is required until the last serial PK blood and plasma sample are obtained on Day 29 of Week 5 (Treatment Continuation Period). Once the last serial PK sample is obtained, dosing of study treatments can occur anytime during the day. For subjects who wish to switch to evening dosing, the subject is to delay their next doses of study treatments by 12 hrs.

Dosing at Home: On days when subjects do not have a scheduled study visit in the clinic subjects will be instructed to self-administer their doses of study treatments at home under fasted conditions, at least 1 hr before or 2 hrs after a meal.

Dosing during the Enzalutamide Run-In Period (Days 1-14): Enzalutamide is the only study treatment taken during the Run-In Period. The intent of this Enzalutamide Run-In Period is to achieve near-steady state plasma concentrations of enzalutamide prior to initiating combination therapy with GSK2636771. Subjects should be instructed to take their once daily dose of enzalutamide every morning at the same time each day if possible (24-hr intervals) during the Enzalutamide Run-In Period. Specific instructions for the administration of enzalutamide on Day 14 of the Enzalutamide Run-In Period are provided in the *Dosing on PK Sampling Days during the Dose Escalation Phase* section below.

Dosing on Scheduled Study Visit Days: Most of the scheduled study visit days during the first 5 weeks of combination treatment will require a pre-dose blood, plasma, and/or urine sample for analysis of PK, CTC, and/or urine electrolytes. On Day 1 of Weeks 8 and 12 during the Treatment Continuation Period, pre-dose blood and plasma samples for analysis of PK are required. On Day 1 of Week 8 and every 8 weeks thereafter during the Treatment Continuation Period, pre-dose blood and urine samples for analysis of CTC (through Week 32 only) and urine electrolytes are also required. Subjects should be instructed to withhold their doses of study treatments on mornings of these scheduled study visits as follows:

Dosing on PK Sampling Days during the Dose Escalation Phase:

- **Day 14 (Enzalutamide Run-In Period);** the day prior to administration of the first dose of GSK2636771)**:** Subjects will fast overnight (at least 8 hrs) and remain fasting the morning of this study visit. Subjects will be instructed to withhold their dose of enzalutamide on the morning of this study visit. After the pre-dose PK plasma sample is drawn, subjects will be administered their doses of enzalutamide in the clinic and will ~~to~~ continue fasting for an additional 2 hrs.

- **Day 29, Week 5 (Treatment Continuation Period):** Subjects will fast overnight (at least 8 hrs) and remain fasting the morning of this study visit. Subjects will be instructed to withhold their doses of study treatment on the morning of this study visit. After the pre-dose PK blood and plasma samples are drawn, subjects will be administered their doses of study treatments in the clinic and will continue fasting for an additional 2 hrs.

- **Weeks 8 and 12 (Treatment Continuation Period):** Subjects will be instructed to withhold their doses of study treatment prior to these study visits. After the pre-dose PK blood and plasma samples are drawn, subjects will be administered their doses of study treatments in the clinic under fasted conditions, at least 1 hr before or 2 hrs after a meal (an overnight fast is not required).

Dosing on PK Sampling Days during the Dose Expansion Phase:

- **Day 29, Week 5 (Treatment Continuation Period) :**

- Subjects scheduled for a *morning* clinic visit will be instructed to withhold the doses of study treatments prior to this study visit. After the pre-dose PK blood and plasma samples are drawn, subjects will be administered their doses of study treatments in the clinic under fasted conditions, at least 1 hr before or 2 hrs after a meal (an overnight fast is not required).

- Subjects scheduled for an *afternoon* clinic visit will be instructed to take their doses of study treatments at the usual time on the morning of this study visit, at least 1 hr before or 2 hrs after a meal (an overnight fast is not required).

- **Weeks 8 and 12 (Treatment Continuation Period):** Subjects will be instructed to withhold the doses of study treatment prior to the study visit during Weeks 8 and 12. Subjects will have their doses of study treatments administered in the clinic after the pre-dose blood draw is completed and under fasted conditions, at least 1 hr before or 2 hrs after a meal.

Dosing on CTC and Urine Electrolyte Sampling Days: Subjects will be instructed to withhold their doses of study treatments on the morning of study visits when a blood or urine sample is to be obtained for analysis of CTCs and/or urine electrolytes, respectively. After the pre-dose blood sample is drawn and/or the pre-dose urine sample is collected, subjects will have their doses of study treatments administered in the clinic, at least 1 hr before or 2 hrs after a meal (an overnight fast is not required).

Vomiting: If a subject vomits after taking study treatment(s), the subject should be instructed NOT to retake the dose and should take the next scheduled dose of study treatment(s). ***If vomiting persists***, the subject should contact the investigator.

Missed Doses: If subject misses a dose of study treatment(s), the subject should be instructed to take the missed dose as soon as they realize it was missed, but not take the missed dose if there are less than 12 hrs until the next dose. The missed dose should be recorded in the subject diary for either GSK2636771 or enzalutamide and in the eCRF.

Capsules: GSK2636771 and enzalutamide capsules should be swallowed whole and not chewed, opened, or dissolved.

6.3.1. GSK2636771

For this study, the starting dose of GSK2636771 is 300 mg taken orally once daily.

GSK2636771 is to be administered within 5 minutes prior to enzalutamide and under fasted conditions, either 1 hr before or 2 hrs after a meal and with approximately 200 mL of water (unless otherwise instructed in Section 6.3.1 for study visit days when PK, CTC, or urine electrolyte sampling is required).

Subjects shall abstain from ingestion of any food or drink containing grapefruit and grapefruit juice, Seville oranges or pomelos within 7 days prior to the first dose of GSK2636771 (Week 1, Day 1 of Combination Treatment Period) until the last dose of study treatment.

6.3.2. Enzalutamide

Per the product prescribing information for enzalutamide [Xtandi, 2016], the recommended dose of enzalutamide 160 mg (four 40 mg capsules) taken orally once daily will be administered during this study.

Enzalutamide may be taken with or without food on each day of the Enzalutamide Run-In Period (Days 1-13). Specific instructions for the administration of enzalutamide on Day 14 of Enzalutamide Run-In Period may be found in Section 6.3.2. Once combination therapy (GSK2636771 + enzalutamide) begins on Week 1, Day 1 of the Combination Treatment Period of both the Dose Escalation Phase and the Dose Expansion Phase, enzalutamide is to be administered within 5 minutes after the administration of GSK2636771 and under fasted conditions, either 1 hr before or 2 hrs after a meal (unless otherwise instructed in Section 6.3.2 for study visit days when PK, CTC, or urine electrolyte sampling is required).

6.4. Handling and Storage of Study Treatments

Handling: Under normal conditions of handling and administration, the study treatments are not expected to pose significant safety risks to site staff. Material Safety Data Sheets (MSDS) for GSK2636771 and enzalutamide describing the occupational hazards and recommended handling precautions will be provided to site staff within the SRM.

Adequate precautions must be taken to avoid direct contact with the investigational product. In the case of unintentional occupational exposure notify the study monitor, the GSK Medical Monitor and/or the study manager.

Storage: All study treatments (GSK2636771 and enzalutamide) must be stored in a secure area under the following conditions for each product:

- GSK2636771: Store under appropriate physical conditions for the product as stated on the label. Refer to the SRM regarding temperature excursions.
- Enzalutamide (Xtandi): Store under appropriate physical conditions for the product as stated on the label. Refer to the SRM regarding temperature excursions.

Access to and administration of study treatments will be limited to the investigator and authorized site staff. Study treatments must be dispensed or administered only to subjects who qualify for entry in this study and in accordance with the protocol. Subjects should be reminded that all study treatments should be stored at home out of the reach of children.

6.5. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount

returned by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study. Refer to the SRM for further detailed instructions on product accountability.

6.6. Treatment Compliance

Compliance with study treatments will be assessed through querying the subject during the site visits and documented in the source documents and eCRF.

A record of the number of GSK2636771 capsules and enzalutamide capsules dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates including dates for treatment delays and/or dose reductions will also be recorded in the eCRF.

6.7. Treatment of Study Treatment Overdose

In the event of a GSK2636771 or enzalutamide overdose (defined as administration of more than the protocol-specified dose), the investigator should contact the GSK Medical Monitor immediately and closely monitor the subject for AEs/SAEs and laboratory abnormalities.

Subjects suspected of overdose should be monitored at least until through five t1/2 of each study treatment, and resolution of all AEs and laboratory abnormalities suspected to be related to study treatment.

In the case of treatment overdose, decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the GSK Medical Monitor.

A plasma or blood sample for PK analysis of one or more study treatments may be requested by the GSK Medical Monitor on a case-by-case basis. This plasma or blood sample should be collected as soon as possible, but within 7 days from the date of the last dose of study treatment (or suspected overdose).

Information regarding the suspected overdose administered should be documented in the eCRF.

7. DOSE MODIFICATIONS, STOPPING CRITERIA AND MANAGEMENT GUIDELINES

The following dose modifications, stopping criteria, and management guidelines for specific events associated with GSK2636771 are provided as guidance and should not act as a replacement for sound clinical judgment. The investigator should use clinical judgment to determine which study treatment may be contributing to the toxicity necessitating dose adjustment, and make the appropriate change for that agent. The severity of AEs will be graded utilizing the CTCAE v4.0.

If a given toxicity is considered to be related to one specific study treatment by the investigator but not both, then dose modification should only occur with the study treatment associated with the specific toxicity or event of clinical concern.

7.1. Dose Modifications

7.1.1. GSK2636771

Dose modification guidelines for GSK2636771 are outlined in Table 4 for clinically significant toxicities that are deemed related to study treatment but are not addressed specifically in Section 7.3.

Dose re-escalation of GSK2636771 may be considered for some subjects who are clearly benefiting from treatment but must be discussed and agreed with the GSK Medical Monitor.

Table 4 Dose Modification for GSK2636771

Toxicity Grade	Dose Modification of GSK2636771
Grade 1	Continue at current dose level. Consider supportive care.
Grade 2	Consider withholding dose until toxicity resolves to Grade 1 or baseline. Upon resolution, then restart at current dose level. Consider supportive care.
Grade 3	Withhold dose until toxicity resolves to Grade 1 or baseline. Upon resolution, then consider dose reducing by next lower dose level. Consider supportive care.
Grade 4	Permanently discontinue study treatment.

GSK2636771: The dose of GSK2636771 should be adjusted in increments of 100 mg. Table 5 below illustrates an example using the starting dose of 300 mg once daily.

Table 5 Dose Levels for GSK2636771

Dose Level	GSK2636771 Dose (mg)
Starting dose	300
Dose Level -1	200
Dose Level -2	100

7.1.2. Enzalutamide

If a subject experiences a Grade 3 or greater toxicity or an intolerable side effect, treatment with enzalutamide should be held for 7 days or until the event resolves to Grade 2 or less. Then, treatment with enzalutamide may be resumed at the same dose level (160 mg [4 capsules]) or at a reduced dose of 120 mg (3 capsules) or 80 mg (2 capsules) or per local prescribing information, if warranted.

7.2. Stopping Criteria

7.2.1. QTc Stopping Criteria

- QTc >500 msec

OR

- Change from baseline of QTc >60 msec

For subjects with underlying BBB, follow the discontinuation criteria listed below:

Baseline QTc with BBB	Discontinuation QTc with BBB
<450 msec	>500 msec
450 – 480 msec	≥530 msec

7.2.2. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the US FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

7.2.2.1. Liver Chemistry Stopping and Increased Monitoring Algorithm for Subjects <u>WITH</u> entry criteria ALT ≤2.5xULN

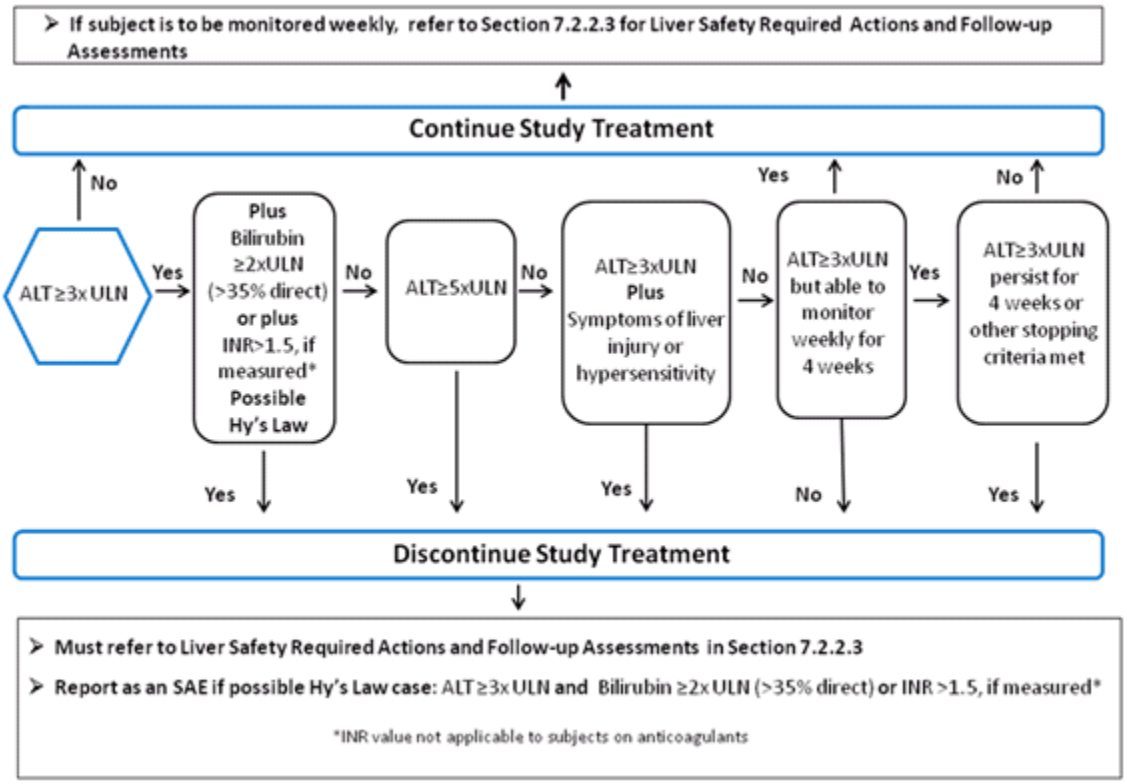

Table 6 Liver Chemistry Stopping Criteria – Liver Stopping Event for Subjects WITH Entry Criteria ALT ≤2.5xULN

ALT absolute	ALT ≥5xULN
ALT Increase	ALT ≥3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥3xULN **and** bilirubin ≥2xULN (**>**35% direct bilirubin)
INR[2]	ALT ≥3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥3xULN **and** cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Abbreviations: ALT, alanine aminotransferase; INR, international normalization ratio; SAE, serious adverse event; ULN, upper limit of normal

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥3xULN and bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).

7.2.2.2. Liver Chemistry Stopping and Increased Monitoring Algorithm including Subjects WITH Documented Liver Metastases/Tumor Infiltration at Baseline AND entry criteria ALT>2.5xULN but ≤5xULN

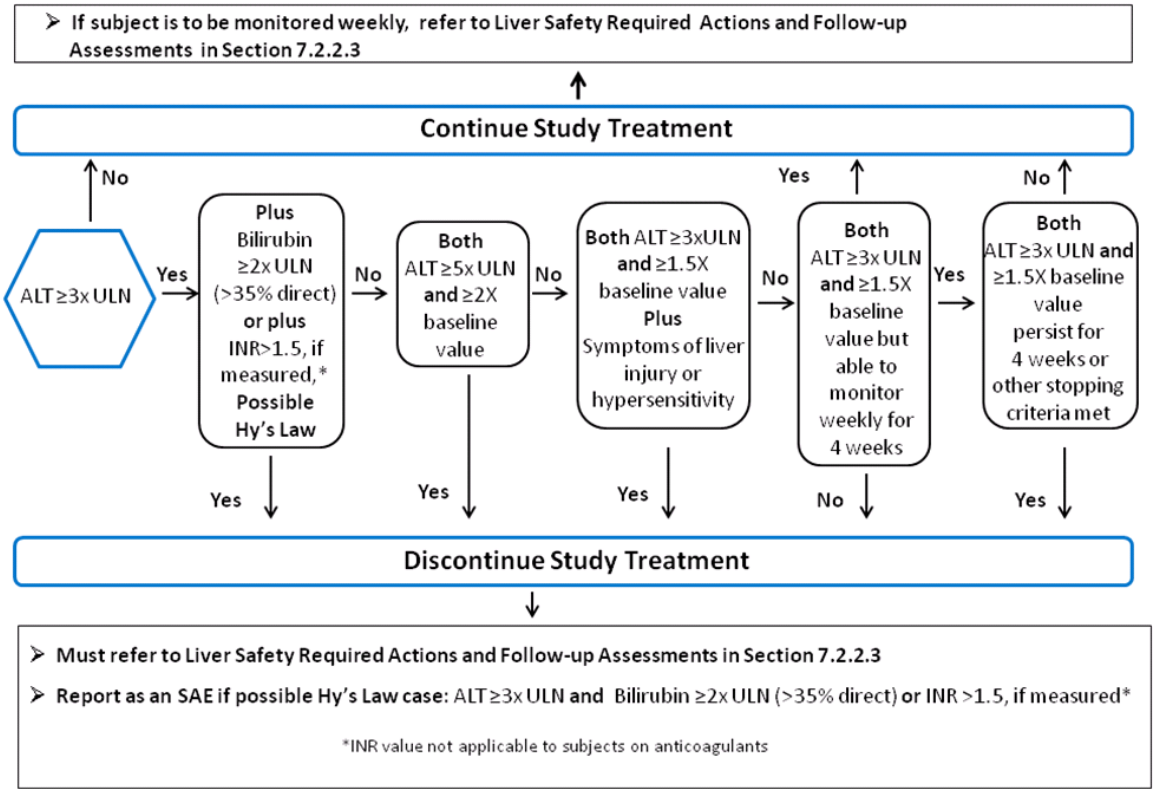

Table 7 Liver Chemistry Stopping Criteria – Liver Stopping Event for Subjects with Documented Liver Metastases/Tumor Infiltration at Baseline AND Entry Criteria ALT>2.5xULN but ≤5xULN

ALT absolute	**Both** ALT ≥5xULN **and** ≥2x baseline value
ALT Increase	**Both** ALT ≥3xULN **and** ≥1.5x baseline value that persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
INR[2]	ALT ≥3xULN **and** INR>1.5, if INR measured
Cannot Monitor	**Both** ALT ≥3xULN **and** ≥1.5x baseline value that cannot be monitored for 4 weeks
Symptomatic[3]	**Both** ALT ≥3xULN **and** ≥1.5x baseline value associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Abbreviations: ALT, alanine aminotransferase; INR, international normalization ratio; SAE, serious adverse event; ULN, upper limit of normal

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥3xULN **and** bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick,** indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis);** INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).

7.2.2.3. Liver Safety Required Actions and Follow-up

Table 8 Required Actions and Follow-Up Assessments Following ANY Liver Stopping Event

Actions	Follow-Up Assessments
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hrs** • Complete the liver event eCRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow-up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol	• Viral hepatitis serology[1] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[3] • Blood sample for PK analysis, obtained 24-72 hrs after last dose[4] • Serum creatine phosphokinase and lactate dehydrogenase. • Fractionate bilirubin, if total bilirubin ≥2xULN

Actions	Follow-Up Assessments
and GSK Medical Governance approval **is granted** (refer to Appendix 6) • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow-up assessments **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase and bilirubin) and perform liver event follow-up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE eCRF • Record use of concomitant medications on the concomitant medications eCRF including acetaminophen, herbal remedies, other OTC medications • Record alcohol use on the liver event alcohol intake eCRF **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins. • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, MRI or CT) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRFs

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; DNA, deoxyribonucleic acid; eCRF, electronic case report form; GSK, GlaxoSmithKline; HPLC, high performance liquid chromatography; hrs, hours; IgG/IgM, immunoglobulin G or M; INR, international normalization ratio; MRI, magnetic resonance imaging; OTC, over-the-counter; PCR, polymerase chain reaction; PK, pharmacokinetic; RNA, ribonucleic acid; SAE, serious adverse event; SRM, Study Reference Manual; ULN, upper limit of normal

1. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
2. All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
4. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Table 9 Liver Chemistry Increased Monitoring Criteria with Continued Therapy

Criteria	Actions
Subject with entry criteria ALT≤2.5xULN ALT ≥3xULN **but** <5xULN **and** bilirubin <2xULN, **without** symptoms believed to be related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks **Subject with documented liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5xULN but ≤5xULN** ALT ≥3xULN and 1.5x baseline value **but** ALT <5xULN and 2x baseline value **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury, or hypersensitivity **and** who can be monitored weekly for 4 weeks	• Notify the GSK Medical Monitor **within 24 hrs** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above **For subjects with entry criteria ALT≤2.5xULN** • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline. **For subjects with documented liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5xULN but ≤5xULN** • If, after 4 weeks of monitoring, ALT <3xULN and <1.5x baseline value, and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GSK, GlaxoSmithKline; hrs, hours; ULN, upper limit of normal

Refer to Appendix 6 for liver safety drug restart or rechallenge guidelines.

7.2.3. Left Ventricular Ejection Fraction (LVEF) Stopping Criteria

Echocardiography (or multigated acquisition [MUGA] scan) must be performed at Screening and as clinically indicated as outlined in the Time and Events Tables (Section 8.1). Subjects who have an absolute decrease of >10% in LVEF compared with baseline and the ejection fraction is below the institution's lower limit of normal (LLN) should temporarily discontinue treatment with GSK2636771 and have a repeat evaluation of LVEF within 1 week. Echocardiogram (ECHO) or MUGA should be repeated every 1 to 2 weeks for 4 weeks or until LVEF recovery to above institutional LLN and within 10% of baseline.

- If the LVEF recovers (defined as ≥LLN and absolute decrease ≤10% compared with baseline) at any time during the next 4 weeks, after consultation and approval of the GSK Medical Monitor, the subject may be restarted on GSK2636771 at a reduced dose. For such subjects, monitoring of LVEF will be

performed 2 and 4 weeks after re-challenge, and every 4 weeks thereafter for a total of 16 weeks and then per protocol.

- If repeat LVEF does not recover within 4 weeks, treatment with GSK2636771 should be permanently discontinued. Ejection fraction should be monitored every 4 weeks for a total of 16 weeks or until resolution.

Subjects with Grade 3 or 4 (symptomatic) left ventricular systolic dysfunction must discontinue treatment with GSK2636771. Ejection fraction should be monitored every 4 weeks for a total of 16 weeks or until resolution. If recovery occurs (LVEF >institutional LLN and symptom resolution) within 4 weeks, treatment with GSK2636771 may be restarted at a reduce dose in consultation with the GSK Medical Monitor.

Copies of all ECHOs (or MUGA scans) and cardiology consultations performed on subjects who experience a >10% decrease in LVEF from baseline and whose cardiac ejection fraction is <institution's LLN will be required by GSK for review. Instructions for submitting qualifying ECHOs (or MUGA scans) are provided in the SRM.

7.2.4. Valvular Toxicity Stopping Criteria

Subjects who have a new asymptomatic, moderate regurgitation or stenosis by ECHO or MUGA scan (Grade 2 mitral/tricuspid/aortic valvular toxicity per CTCAE v4.0 should temporarily discontinue treatment with GSK2636771 and have a repeat evaluation by ECHO within 1 week. An ECHO (or MUGA scan) should be repeated every 1 to 2 weeks for 4 weeks or until valve recovery to baseline.

- If the valve recovers to baseline any time during the next 4 weeks after consultation and approval of the GSK Medical Monitor, the subject may be restarted on GSK2636771 at a reduced dose(s). For such subjects, monitoring of the valve via ECHO (or MUGA scan) will then be performed 2 and 4 weeks after re-challenge, and every 4 weeks thereafter for 8 weeks and then per protocol.
- If repeat ECHO (or MUGA scan) does not reveal valve recovery to baseline within 4 weeks, then the subject should permanently discontinue GSK2636771. The valve should continue to be monitored via ECHO (or MUGA scan) every 4 weeks for 8 weeks or until resolution.

Subjects with a Grade 3 or 4 (symptomatic, severe regurgitation/stenosis by imaging with symptoms controlled by medical intervention) valvular toxicity must discontinue GSK2636771. Valvular toxicity should continue to be monitored every 4 weeks for 8 weeks or until resolution. If recovery occurs (return to baseline via imaging AND symptom resolution) within 4 weeks, the subject may restart GSK2636771 at a reduced dose after consultation and approval of the GSK Medical Monitor.

Copies of all ECHO(s) (or MUGA scan) and cardiology consultations performed on subjects who experience valvular toxicity will be required by GSK for review. Instructions for submitting qualifying ECHOs (or MUGA scans) are provided in the SRM.

7.3. Management Guidelines for Specific Events Associated with GSK2636771

If a subject experiences an AE during the Enzalutamide Run-In Period resulting in a dose interruption that precludes the subject from completing the run-in period within 14 days or a dose reduction, the GSK Medical Monitor should be contacted as approval will be required in order for the subject to continue in the study (refer to the SRM).

7.3.1. Renal Insufficiency or Other Renal Events

Prior to start of study treatment, concomitant medications should be reviewed for the potential risk of inducing nephrotoxicity and concomitant medications should be modified if clinically possible.

Close monitoring of serum creatinine, calcium and phosphate and treatment interruption for increased serum creatinine >2 mg/dL (or >0.5 mg/dL above baseline), hypocalcemia, and hypophosphatemia, respectively, should occur. Nephrology consultation should also be considered.

Calcium should be carefully managed in all subjects and especially in subjects with bone lesions/metastases and in those on treatments that are associated with hypocalcemia, including but not limited to, bisphosphanates (e.g., zoledronic acid) or denosumab (RANK-L inhibitor). Subjects with baseline calcium levels at or near the lower normal limit and those with Vitamin D below the normal limit should be treated with supplements. Subjects who develop hypocalcemia should be closely monitored and managed per Table 10.

Guidelines regarding the management of renal insufficiency or renal-related events considered to be related to study treatment are provided in Table 10.

Table 10 Management and Dose Modifications for Renal Events

Assessment	Action and Dose Modification
Urine dipstick protein ≥2+	• Monitor for concomitant medications (e.g., NSAIDs) or medical conditions (e.g., urinary tract infection) associated with positive urinary protein dipstick test (see SRM for further details) • Assess BP and ensure it is well-controlled (<140/90 mmHg) • Obtain a random UPC ratio (see Appendix 5)
UPC ratio ≥3	• Repeat UPC within 24 hrs of previous result • If repeat UPC confirms UPC ratio ≥3, permanently discontinue treatment with GSK2636771 • Consult with GSK Medical Monitor
UPC ratio >0.5 but <3	• Repeat UPC within 24 hrs of previous result • If repeat UPC confirms UPC >0.5 but <3, interrupt treatment with GSK2636771 • Evaluate urine sediment (rule out RBC casts) • Consider consult with nephrologist regarding further management • Reassess UPC ratio at least weekly or more frequently if clinically indicated • If UPC ratio improves to ≤0.5 within 14 days:

Assessment	Action and Dose Modification
	• Restart treatment with GSK2636771 with dose reduced one dose level • Continue monitoring UPC ratio weekly for 4 weeks • Resume urinalysis testing at frequency indicated in Time and Events Tables (Section 8.1) • If UPC ratio fails to improve to ≤0.5 within 14 days: • Discontinue treatment with GSK2636771 • Consult with a nephrologist regarding further management • Consult with GSK Medical Monitor • If UPC ratio elevation recurs after one dose level reduction: • Discontinue treatment with GSK2636771; withdraw subject from study unless there is agreement between investigator and GSK Medical Monitor that subject will benefit from continued treatment following recovery of UPC ratio to ≤0.5
UPC ≤0.5	• Continue treatment with GSK2636771 at same dose level without interruption
Serum creatinine ≥0.3 mg/dL (≥26.5 µmol/L) increase from baseline	• Repeat serum creatinine level within 24 hrs of previous result • If repeat value confirms serum creatinine ≥0.3 mg/dL (≥26.5 µmol/L) increase from baseline: • Immediately interrupt treatment with GSK2636771 • Evaluate and treat possible causes for elevated serum creatinine (e.g., renal outflow obstruction, sepsis, dehydration, hypotension, GI bleed, medications [e.g., trimethoprim, ketoconazole or cimetidine] that increase serum creatinine level) • Obtain blood sample for PK analysis , if within 24-72 hrs after the last dose (refer to Section 8.7.3.1 for details on PK sample collection) • Obtain serum chemistries for calcium, phophorus and magnesium • Obtain UA, UPC and urine electrolytes • Consider oral or IV hydration, if clinically indicated; and 24-hour Urine Creatinine Clearance assessment, where feasible • Repeat serum creatinine level every 7 days or more frequently if clinically indicated • If serum creatinine fails to improve (≥0.3 mg/dL [≥26.5 µmol/L] increase persists) within 14 days following dose interruption: • Permanently discontinue treatment with GSK2636771 • Consult with GSK Medical Monitor • If serum creatinine improves (<0.3 mg/dL [<26.5 µmol/L] increase from baseline) within 14 days following dose interruption: • Restart treatment with GSK2636771 with dose reduced by one dose level • Repeat serum creatinine level every 4 weeks or more frequently if clinically indicated • If elevated serum creatinine recurs after one dose reduction (≥0.3 mg/dL [≥26.5 µmol/L] increase from baseline): • Repeat serum creatinine within 24 hrs to confirm result • If repeat serum creatinine confirms increase, withdraw subject from treatment/study unless there is agreement between investigator and GSK Medical Monitor that subject will benefit from continued treatment following recovery of serum creatinine (≤0.3 mg/dL [<26.5 µmol/L] increase from baseline)

Assessment	Action and Dose Modification
	• If repeat serum creatinine fails to confirm increase, continue treatment with GSK2636771 at same dose level without interruption and obtain blood sample for PK analysis , within 24-72 hrs after the last dose (refer to Section 8.7.3.1 for details on PK sample collection)

Hypocalcemia (serum calcium ≥Grade 1) ***or*** Hypophosphatemia (serum phosphate ≥Grade 3 or symptomatic Grade 2)	• Administration of oral calcium supplements to subjects with calcium levels at or near the lower limit of normal should be considered
	• For subjects with Grade1 hypocalcemia, administer oral calcium supplements and evaluate the need for Vitamin D supplementation.
	• For hypocalcemia > Grade 1, repeat serum calcium and Vitamin D, and phosphate level within 24 hrs of previous result
	  • If repeat value confirms > Grade 1 serum calcium, or symptomatic Grade 2 serum phosphate.
	  • Immediately interrupt treatment with GSK2636771
	  • Treat as clinically indicated by local institutional standards or administer i.v. calcium gluconate (1 g/10 ml) and evaluate the need for Vitamin D supplementation.
	  • Obtain serum PTH level
	  • Obtain blood sample for PK analysis, if requested (see SRM), within 24-72 hrs after the last dose (refer to Section 8.7.3.1 for details on PK sample collection)
	  • Obtain urine samples for urine creatinine, calcium, phosphate, and protein at treatment interruption; repeat every 7 days
	  • Repeat serum calcium or phosphate level every 7 days or more frequently if clinically indicated
	• If serum calcium fails to improve to WNL or if serum phosphate fails to improve to asymptomatic Grade 2 within 14 days following dose interruption:
	  • Permanently discontinue treatment with GSK2636771
	  • Consult with GSK Medical Monitor
	• If serum calcium improves to WNL or serum phosphate improves to asymptomatic Grade 2 within 14 days following dose interruption:
	  • Restart treatment with GSK2636771 with dose reduced by one dose level
	  • Repeat serum calcium or phosphate level per Time and Events Tables (Section 8.1) or more frequently if clinically indicated
	• If decreased serum calcium or phosphate levels reoccurs after one dose reduction :
	  • Repeat serum calcium or phosphate levels within 24 hrs to confirm result
	  • If repeat serum calcium or phosphate levels confirm decrease, withdraw subject from treatment/study unless there is agreement between investigator and GSK Medical Monitor that subject will benefit from continued treatment following recovery of serum calcium or phosphate to baseline with dose of GSK2636771 further reduced one dose level.
	• If repeat serum calcium or phosphate fails to confirm a decrease, continue treatment with GSK2636771 at same dose level without interruption

Abbreviations: BP, blood pressure; GI, gastrointestinal; GSK, GlaxoSmithKline; IV, intravenous; mmHg, millimeters of mercury; NSAIDs, non-steroidal anti-inflammatory drugs; PK, pharmacokinetics; PTH, parathyroid hormone; RBC, red blood cell; SRM, Study Reference Manual; UPC, urine/protein/creatinine ratio

Details regarding collection and testing of urine specimens are provided in the SRM.

7.3.1.1. Parathyroid Hormone (PTH)

Serum parathyroid hormone (PTH) level will be assessed on the first day of combination treatment (Week 1, Day 1 of Combination Treatment Period). Subsequently a serum PTH level should be obtained for any subject who experiences Grade 2 or greater hypocalcemia or hypophosphatemia while on study (refer to Table 10).

7.3.2. Cardiac-related Toxicities

Reversible increases in mean arterial pressure **and** decreases in heart rate and cardiac contractility that were considered secondary to an elevation in blood pressure were observed in a single dose safety pharmacology study in dogs administered 300 mg/kg of GSK2636771. In the ongoing FTIH study, no Grade 3 or higher cardiac events have been observed. Subjects with a history of uncontrolled hypertension, heart failure, or known significant coronary artery disease are excluded from this study. Cardiac monitoring, including assessment of BP and heart rate, along with 12-lead ECGs, will be performed.

7.3.2.1. Hypertension

Hypertension is defined as a pathological increase in BP; a repeatedly elevated BP exceeding 140/90 mmHg. Hypertension has been reported with GSK2636771; however, the mechanism by which it may cause hypertension has not been established. It should be noted that hypertension may resolve as the study treatment is cleared and that there may be a risk for rebound hypotension. Any time antihypertensive medication(s) is/are adjusted, ambulatory BP monitoring should be considered.

Table 11 Management and Dose Modification for Hypertension

Grade[1]	Action and Dose Modification
Grade 1: SBP 120 - 139 mmHg or DBP 80 - 89 mmHg	1) No interruption in treatment with GSK2636771; maintain current dose. 2) Careful monitoring of BP. Ambulatory BP monitoring should be considered.
Grade 2: SBP 140 - 159 mmHg or DBP 90 -99 mmHg, medical intervention may be indicated	1) No interruption in treatment with GSK2636771; maintain current dose. 2) Begin antihypertensive medication(s), adjust dose of current antihypertensive medication(s), or begin an additional antihypertensive medication(s). 3) Titrate antihypertensive medication(s) during next 2 weeks until hypertension ≤Grade 1. 4) If hypertension is not ≤Grade 1 within 2 weeks, follow steps outlined for Grade 3.
Grade 3: SBP ≥160 mmHg or DBP ≥100 mmHg, medical intervention indicated	1) Interrupt treatment with GSK2636771. 2) Begin antihypertensive medication, or adjust dose of current antihypertensive medication(s), or begin an additional antihypertensive medication(s). 3) Titrate antihypertensive medication(s) during next 2 weeks as indicated until hypertension ≤Grade 1. Restart study treatment at a previously evaluated dose with at least a with a 25% dose reduction. 5) If hypertension is not ≤Grade 1 within 2 weeks, permanently discontinue treatment with GSK2636771 and follow-up per protocol.
Grade 4: Life-threatening, malignant hypertension, urgent intervention indicated	Permanently discontinue treatment with GSK2636771 and follow-up per protocol.

Abbreviations: BP, blood pressure; CTCAE, Common Terminology Criteria for Adverse Events; DBP, diastolic blood pressure; mmHg, millimeters of mercury; SBP, systolic blood pressure

1. Grading is based on CTCAE v4.0.

7.3.3. Rash

Subjects should be informed to protect themselves against direct sun exposure and to avoid exposure to known allergens. Subjects should contact the investigator immediately upon onset of a rash. Full supportive care should be provided to subjects who experience a rash while on study. *Information contained in this section is a guideline. The investigator's best medical judgment should determine medical intervention for rash*.

Table 12 Management and Dose Modification for Rash

	1st Occurrence	2nd Occurrence	3rd Occurrence
Grade 1[3]	• Symptomatic care[1] • Consider oral steroids if multiple occurrences[2]		
Grade 2[3]	• Consider oral steroids[2]	• Consider oral steroids[2] • Hold study treatment until <Grade 1, then resume at full dose	• Administer oral steroids[2] • Hold study treatment until ≤Grade 1 then restart treatment with GSK2636771 with dose reduced **one** dose level.
Grade 3[3, 4]	• Consider oral steroids[2] • Hold study treatment until ≤Grade 1, then resume at full dose	• Administer oral steroids[2] • Hold study treatment until ≤Grade 1 then restart treatment with GSK2636771 with dose reduced **one** dose level.	• Administer oral steroids[2] • Hold study treatment until ≤Grade 1 then restart treatment with GSK2636771 with dose reduced **2** dose levels.
Grade 4[3, 4]	• Administer oral steroids[2] • Hold study treatment until ≤Grade 1 then restart treatment with GSK2636771 with dose reduced **one** dose level.	• Administer oral steroids[2] • Hold study treatment until ≤Grade 1 then restart treatment with GSK2636771 with dose reduced **2** dose levels.	• Discontinue treatment with GSK2636771.

1. Recommended symptomatic measures (for all grades) includes topical steroids (e.g., hydrocortisone 1% or 2.5% cream), antihistamines, hypoallergenic moisturizers and emollients for dry skin (e.g., 5 -10% urea in cetomacrogel cream or soft paraffin).
2. Oral steroid therapy should follow institutional standard of care (e.g., short course of tapering dose of methylprednisolone or prednisone).
3. Dermatology consult should be considered for ≥Grade 3 rash or multiple occurrences of ≤Grade 2.
4. Obtain blood sample for PK analysis, if within 24-72 hours after the last dose (see Section 8.7.3.1).

7.3.4. Diarrhea

Episodes of diarrhea have occurred in subjects receiving GSK2636771 monotherapy. Other frequent causes for diarrhea, including concomitant medications (e.g., stool softeners, laxatives, antacids, etc.), infections by *C. difficile* or other pathogens, partial bowel obstruction, should be clinically excluded.

Standardized and universal guidelines have been developed by an American Society of Clinical Oncology (ASCO) panel for treating chemotherapy-induced diarrhea [Benson, 2004]. Presented in the sections below are the recommended guidelines for the management of diarrhea in subjects receiving GSK2636771. These guidelines were derived from the recommendations published by the ASCO panel [Benson, 2004].

Early identification and intervention is critical for the optimal management of diarrhea. A subject's baseline bowel patterns should be established so that changes in patterns can be identified while subject is on treatment.

An assessment of frequency, consistency and duration as well as knowledge of other symptoms such as fever, cramping, pain, nausea, vomiting, dizziness and thirst should be taken at baseline. Consequently subjects at high risk of diarrhea can be identified. Subjects should be educated on signs and symptoms of diarrhea with instructions to report any changes in bowel patterns to the physician.

It is recommended that subjects keep a diary and record the number of diarrhea episodes and its characteristics. They should also include information on any dietary changes or other observations that may be useful in the evaluation of their diarrhea history.

If subjects present with diarrhea of any grade, check they are receiving the study treatment correctly (i.e., single dose, rather than splitting it through the day). Obtain information on food (solid and liquid) and over-the-counter (OTC) medication(s), including herbal supplements, taken during the treatment period.

Guidelines regarding management and dose reduction for diarrhea considered to be related to study treatments by the investigator are provided in Table 13. Also, see guidance on hydration in Section 11.3.

Table 13 Management and Dose Modification Guidelines for Diarrhea

Grade	Management	Action and Dose Modification
Uncomplicated Diarrhea - Grade 1	1. Instruct subject to start supportive care immediately at the first episode of diarrhea (i.e., unformed stool) and contact the investigator. • Administer loperamide: Initial dose: 4 mg. Subsequent doses: 2 mg after each unformed stool 1. Re-evaluate after 24 hrs: 2. *If diarrhea is resolving:* continue loperamide treatment at 2 mg dose after each unformed stool until diarrhea-free (i.e., bowel patterns return to baseline) for 12 hrs. If diarrhea recurs, re-initiate loperamide as needed to maintain normal bowel pattern. 3. *If diarrhea is NOT resolving:* continue loperamide 2 mg every 4 hrs for the next 24 hrs; re-evaluate after 24 hrs. If not resolving, administer loperamide 2 mg after each unformed stool until diarrhea free (i.e., bowel patterns return to baseline) for 12 hrs. If diarrhea is not resolving, continue loperamide 2 mg every 4 hrs and re-evaluate every 24 hrs. 2. Dietary modifications: 4. Stop all lactose containing products and eat small meals 5. Avoid spicy, fried and fatty foods, raw vegetables and other foods high in fiber 6. Avoid caffeine and alcohol (can irritate bowel and increase motility) 7. Hydration: Drink 8 to 10 large glasses of clear liquids (e.g., water, electrolyte drink) daily. Avoid acidic drinks such as tomato juice and fizzy soft drinks 8. Supplement diet to include food rich in potassium (e.g., bananas, potatoes, apricots; evaluate their impact on diarrhea due to fiber content (e.g., apricots)	• Continue study treatments at current dose. • Continue supportive care until diarrhea resolves (diarrhea free for 12 hrs and bowel pattern returns to baseline) • If diarrhea recurs after stopping loperamide treatment, resume loperamide treatment, re-introduce diet modifications, and continue study treatments at current dose.

Grade	Management	Action and Dose Modification
Uncomplicated Diarrhea - Grade 1 ***continued***	3. If Grade 1 diarrhea persists for >1 week with loperamide treatment, consider treatment with second-line agents (i.e., octreotide, budesonide or tincture of opium). 4. If Grade 1 diarrhea persists for ≥2 weeks, refer to Persistent Grade 2 diarrhea management guidelines.	
Uncomplicated Diarrhea – Grade 2	1. Instruct subject to start supportive care immediately at the first episode of diarrhea (i.e., unformed stool) and contact the investigator. 9. Administer loperamide: Initial dose: 4 mg. Subsequent doses: 2 mg every 4 hrs or after each unformed stool 10. Re-evaluate after 24 hrs: 11. *If diarrhea is resolving:* continue loperamide treatment at 2 mg dose after each unformed stool until diarrhea free (i.e., bowel patterns return to baseline) for 12 hrs. If diarrhea recurs, re-initiate loperamide as needed to maintain normal bowel pattern. 12. *If diarrhea is NOT resolving:* consider loperamide 2 mg every 2 hrs for the next 24 hrs. If Grade 2 diarrhea persists after 48 hrs of loperamide treatment, start treatment with second-line agents (i.e., octreotide, budesonide or tincture of opium). Consider performing stool work-up, CBC, electrolytes and other tests as appropriate. 2. Dietary modifications: 13. Stop all lactose containing products and eat small meals 14. Avoid spicy, fried and fatty foods, bran, raw vegetables and other foods high in fiber. Eat foods low in fiber (i.e., lean meat, rice, skinless chicken or turkey, fish, eggs, canned or cooked skinless fruits, cooked/pureed vegetables) 15. Avoid caffeine and alcohol (can irritate bowel and increase motility) 16. Hydration: Drink 8 to 10 large glasses of clear liquids (e.g., water, electrolyte drink) daily. Avoid acidic drinks such as tomato juice and fizzy soft drinks	• Continue study treatments at current dose. • Continue supportive care until diarrhea resolves (diarrhea free for 12 hrs / bowel pattern returns to baseline) • Once diarrhea has resolved, subject may gradually re-introduce foods from their normal diet. • If diarrhea recurs after stopping loperamide treatment, resume loperamide treatment, re-introduce diet modifications, and continue study treatments at current dose.

Grade	Management	Action and Dose Modification
Uncomplicated Diarrhea – Grade 2 ***continued***	17. Supplement diet to include food rich in potassium (e.g., bananas, potatoes, apricots); evaluate their impact on diarrhea due to fiber content (e.g., apricots) 18. If diarrhea recurs, refer to Recurrent Diarrhea management guidelines.	
Persistent (≥3 days/ 72 hrs) Diarrhea – Grade 2	1. If Grade 2 diarrhea persists for ≥3 days or 72 hrs, resume loperamide treatment and re-introduce diet modifications. 2. If supportive care measures and interruption of study treatments are ineffective in treatment of persistent Grade 2 diarrhea, perform stool work-up, CBC, electrolytes, and other tests as appropriate. Consider consultation with GI specialist.	• Hold treatment with GSK2636771 and enzalutamide until symptoms have resolved to Grade 1 or baseline bowel pattern. • Once diarrhea has resolved, continue treatment with GSK2636771 and enzalutamide at reduced dose.
Recurrent Diarrhea (>1 occurrence) - (Grade 2)	If second occurrence of Grade 2 diarrhea recurs, resume loperamide treatment and re-introduce diet modifications.	• Once diarrhea resolves to Grade 1 or baseline, consider re-starting study treatments (GSK2636771 + enzalutamide) at a reduced dose
Complicated Diarrhea[2] – Grade 3 or Grade 1 or 2 with complicating factors	1. Instruct subject that they **must** call investigator immediately for any complicated severe diarrhea event. 2. If loperamide has not been initiated, initiate loperamide immediately. Initial dose: 4 mg. Subsequent doses: 2 mg every 2 hrs or after each unformed stool**.** 3. Refer to the dietary modifications for Grade 1 and 2 uncomplicated diarrhea (above). 4. For dehydration use IV fluids as appropriate. If subject presents with severe dehydration, administer octreotide. 5. Perform stool work-up, complete blood count, electrolytes and other tests as appropriate 6. Administer antibiotics (i.e., fluoroquinolones) as needed, especially if diarrhea is persistent beyond 24 hrs or if fever or Grade 3 or 4 neutropenia is present	• Hold treatment with GSK2636771 and enzalutamide until symptoms have resolved to Grade 1 or baseline bowel pattern and without complicating factors present. • Once diarrhea resolves to Grade 1 or baseline, consider re-starting study treatments (GSK2636771 +enzalutamide) at a reduced dose • Continue supportive care until diarrhea resolves (diarrhea free for 24 hrs and bowel pattern returns to baseline)

Grade	Management	Action and Dose Modification
Complicated Diarrhea[2] – Grade 3 or Grade 1 or 2 with complicating factors ***continued***	7. Instruct subject that they **must** call investigator immediately for any complicated severe diarrhea event. 8. If loperamide has not been initiated, initiate loperamide immediately. Initial dose: 4 mg. Subsequent doses: 2 mg every 2 hrs or after each unformed stool**.** 9. Refer to the dietary modifications for Grade 1 and 2 uncomplicated diarrhea (above). 10. For dehydration use IV fluids as appropriate. If subject presents with severe dehydration, administer octreotide. 11. Perform stool work-up, complete blood count, electrolytes and other tests as appropriate 12. Administer antibiotics (i.e., fluoroquinolones) as needed, especially if diarrhea is persistent beyond 24 hrs or if fever or Grade 3 or 4 neutropenia is present 13. Intervention may require hospitalization for subjects most at risk for life threatening complications.	
Complicated Diarrhea – Grade 4	1. Instruct subject that they **must** call investigator immediately for any complicated Grade 4 diarrhea event. 2. If loperamide has not been initiated, initiate loperamide immediately. Initial dose: 4 mg. Subsequent doses: 2 mg every 2 hrs or after each unformed stool**.** 3. For dehydration use IV fluids as appropriate. If subject presents with severe dehydration, administer octreotide. 4. Perform stool work-up, CBC, electrolytes and other tests as appropriate 5. Consider consultation with GI specialist. 6. Administer antibiotics (i.e., fluoroquinolones) as needed, especially if diarrhea is persistent beyond 24 hrs or if fever or Grade 3 or 4 neutropenia is present 7. Intervention may require hospitalization for subjects most at risk for life threatening complications.	• Hold treatment with GSK2636771 and enzalutamide • Consult with GSK Medical Monitor to discuss subject's event history, re-initiation of study treatments, and dose modifications, once symptoms have resolved to Grade 1 or baseline bowel pattern • Continue supportive care until diarrhea resolves (diarrhea free for 24 hrs and bowel pattern returns to baseline)

Abbreviations: CBC, complete blood count; GI, gastrointestinal; hrs, hours; IV, intravenous; mg, milligram(s)

7.3.5. Vomiting

Table 14 Management and Dose Modification for Events of Vomiting

Grade	Action and Dose Modification
≤Grade 1	Continue study treatments at current dose.
Grade 2	Hold until ≤Grade 1. Resume study treatments at same dose level.
Grade 3	Hold[1] until <Grade 2. Resume study treatments at one dose level lower, if indicated.[2]
Grade 4	Withdraw study treatments.

1. Subjects requiring a delay of >14 days should be withdrawn from treatment and/or study.
2. Subjects requiring >2 dose reductions should be withdrawn from treatment and/or study.

It is recommended that any event of vomiting should be managed with the use of antiemetics. Also, see guidance on hydration in Section 11.3.

8. STUDY ASSESSMENTS AND PROCEDURES

This section lists the parameters of each planned study assessment. The timing of each assessment for the Dose Escalation Phase is listed in the Time and Events Table (Section 8.1). Further details for study procedures and assessments can be found in the SRM.

The timing and number of planned study assessments, including safety, PK, and biomarker assessments, may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak blood concentrations) to ensure appropriate monitoring. Any addition or deletion of a study assessment, including any significant change in the timing or frequency of an assessment, must be approved and documented by GSK, and will require a protocol amendment, except in a situation where additional assessments are required to immediately address any safety concerns. The institutional review board (IRB)/independent ethics committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme. No more than 500 mL of blood will be collected over a period of 30 days, including any extra assessments that may be required.

Whenever vital signs, 12-lead ECGs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, and then blood draws (see SRM for additional details).

Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

8.1. Time and Events Tables

This section consists of the Time and Events Tables and supplemental footnotes to describe the assessment windows and sequencing of study-specific assessments and procedures.

Additional unplanned blood, plasma and/or optional tumor samples may be requested with patient consent and investigator agreement as needed to better characterize safety and response(s) in subjects.

Table 15 Time and Events Table for Dose Escalation Phase

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**		**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression[31]**	**Post-Treatment Follow-Up Visit[28]**	**Extended Follow-Up Visits[29]**	**Post-Extended Follow-Up /EOS Visit[30]**
		Day -14 to Day -1	Day 1 to Day 13	Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Wk 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window					*+1 day*	*±1 day*	*±1 day*	*±1 day*	*±1 day*	*+5 days Week 12 only; ±3 days for all other visits*	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Clinical Assessments														
Informed Consent	X[3]	X[4]												
Demographics	X													
Medical History		X												
Determination of PTEN Deficiency Status	M[5]													
Safety Assessments														
ECOG PS		X			X		X	X	X	Week 8 and then Q8wks	X	X		X
Physical Exam		X			X					Week 8 and then Q8wks		X		X
Height[8]		X												
Weight		X			X					Week 8 and then Q8wks		X		X
Vital Signs[9]		X			X	X	X	X	X	X		X		X
12-Lead ECG[10]		X[6]						X		Week 8 and then Q8wks		X		X
ECHO/MUGA		X[6,7]			As clinically indicated									
AE Monitoring			Continuous								X[11]	X[11]		
Concomitant Medications		X	Continuous									X		

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**		**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression[31]**	**Post-Treatment Follow-Up Visit[28]**	**Extended Follow-Up Visits[29]**	**Post-Extended Follow-Up /EOS Visit[30]**
		Day -14 to Day -1	Day 1 to Day 13	Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Wk 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window					*+1 day*	*±1 day*	*±1 day*	*±1 day*	*±1 day*	*+5 days Week 12 only; ±3 days for all other visits*	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Laboratory Assessments[12]														
Hematology/ Clinical Chemistry		X[6]			X[33]	X	X	X	X	X		X		X
Ionized Calcium		X[6]			X	X	X	X	X	X		X		X
Vitamin D[34]		X[6]						X				X		X
Coagulation: PT, PTT, INR		X[6]			X			X						
Liver Function Tests		X[6]			X	X	X	X	X	X		X		X
Urinalysis[13] Urine Microscopy[13] UPC[14]		X[6]			X			X		X		X		X
Urine Electrolytes[15]		X[6]			X[33]	X	X	X		Week 8 and then Q8wks		X		
Parathyroid Hormone					X	As clinically indicated[16]								
Bone Markers[35]					X				X	Weeks 12 and 24		X		X
PSA and LDH[32]		X[6]			X					X	X	X		X
Serum Testosterone		X[6]										X		X
PK Assessments														
PK Blood Sampling[17]				X					X	Weeks 8 and 12				
Disease Assessments[18]														
CT Scan or MRI[19]		X[6,7]								Week 8 and then Q8wks to Week 48; then Q12wks	X		X	

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**		**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression[31]**	**Post-Treatment Follow-Up Visit[28]**	**Extended Follow-Up Visits[29]**	**Post-Extended Follow-Up /EOS Visit[30]**
		Day -14 to Day -1	Day 1 to Day 13	Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Wk 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window					*+1 day*	*±1 day*	*±1 day*	*±1 day*	*±1 day*	*+5 days Week 12 only; ±3 days for all other visits*	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Disease Assessments[18] continued														
Chest X-Ray or Chest CT Scan		X[6,7]												
Bone Scan[20]		X[6,7]								Week 12 and then Q12wks	X		X	
Biomarker Assessments														
CTC –- Janssen[21]		X			X			X		Weeks 8, 16, 24, and 32	X			
CTC – EPIC[22]		X								Week 8 only	X			
Predictive Biomarker: Tumor Tissue[23]					X									
Progression Tumor Biopsy[24]											X			
Tumor Biopsies for Pharmaco-dynamics[24]				X		X[24]								
cfDNA/RNA/Soluble Markers[25]		X			X			X		Weeks 8, 16, 24, and 32	X			
Blood Sample for Genetic Research[26]					X									
Study Treatments[27]														
Enzalutamide			Continuous		Continuous									
GSK2636771					Continuous									

Abbreviations: AE, adverse event; cfDNA, circulating-free tumor DNA; CT, computed tomography; CTC, circulating tumor cells; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOS, End of Study; HbA1C, hemoglobin A1C; INR, international normalization ratio; M, mandatory; MRI, magnetic resonance imaging; MUGA, multigated acquisition scan; O, optional; PD, pharmacodynamics; PK, pharmacokinetics; PS, performance status; PSA, prostate-specific antigen; PT, prothrombin time; PTEN, phosphatase and tensin homolog; PTH, parathyroid hormone; PTT, partial thromboplastin time; Q4wks, every 4 weeks; Q8wks, every 8 weeks; Q12wks, every 12 weeks; UPC, urine:protein:creatinine; Wk(s), week(s)

1. **Study Assessments:** All assessments may be performed more frequently if clinically appropriate. Assessments scheduled on days of dosing should be completed prior to the administration of study treatments, unless otherwise specified
2. **Study Assessments:** Assessments throughout the study are calendar based starting from Week 1, Day 1 of the Combination Treatment Period (the first dose of combination treatment). Dose interruptions should not alter the assessment schedule for any subsequent treatment period.
3. **Pre-Screening Informed Consent:** Separate pre-screening informed consent must be obtained prior to initiation of any pre-screening procedures or assessments.
4. **Screening Informed Consent:** Informed consent must be obtained prior to initiation of any screening procedures or assessments..
5. **PTEN Deficiency Status (Mandatory):** Tumor tissue samples (archived or fresh tumor tissue obtained by pre-treatment biopsy) will be collected to determine PTEN deficiency status of the tumor by the designated central laboratory. Refer to the SRM for details about the number of slides to be submitted, preparation, handling and shipping. Results of the PTEN deficiency testing from the central laboratoryonly will be used to determine if the subject is eligible to continue Screening. Only subjects with PTEN deficient tumor based on central laboratorytesting results will be screened. **Any remaining tumor tissue may be used for other predictive biomarker analyses** if consent has been obtained.
6. **Screening:** When possible, screening assessments that require imaging, ECG, ECHO/MUGA, or laboratory studies should be performed AFTER PTEN status has been determined.
7. **Screening:** All screening assessments must be completed and all entry criteria must be met prior to assessments on Day 1 of Enzalutamide Run-In Period. EXCEPTION: ECHO/MUGA must be completed within 28 days of enrollment (Day 1 of Enzalutamide Run-In Period), and disease assessment must be completed within 28 days (35 days if MRI is used) prior to enrollment (Day 1 of the Enzalutamide Run-In Period).
8. **Height** is only measured at Screening**.**
9. **Vital Signs:** Blood pressure, temperature and heart rate will be measured. Vital signs may be measured more frequently if clinically warranted.
10. **ECG:** A single 12-lead ECG is to be performed ***before*** vital signs are measured and any blood draws, if assessments are planned at the same nominal time point.
11. **AE Monitoring:** Continued monitoring of AEs applies only to ongoing events at time of treatment discontinuation.
12. **Laboratory Assessments:** Refer to Section 8.6.6 (Table 17) for list of specific laboratory tests to be performed. Assessments may be performed within 24 hrs prior to scheduled visit (liver function tests and urine tests for UPC may be performed up to 72 hrs prior to a scheduled visit) to ensure availability of results.
13. **Urinalysis and Urine Microscopy:** Urinalysis and urine microscopy will be performed at the time points indicated. Assessments may be performed within 24 hrs prior to a scheduled visit to ensure availability of results.
14. **UPC:** Urine sample for UPC is to be collected at the time points indicated. Perform UPC with the first morning urine specimen (if possible) when urine dipstick protein $\geq$2+. Urine samples for UPC may be collected up to 72 hrs prior to a scheduled visit to ensure that results are available at time of visit. If the urine sample collected at Screening is contaminated with other bodily fluids, UPC will not be determined and subject will remain eligible for the study.
15. **Urine Electrolytes:** Urine samples will be obtained at Screening, pre-dose on Day 1 (Week 1), Day 3 OR Day 4, Day 15 (Week 3), Day 22 (Week 4) of the Combination Treatment Period, Week 8 and then every 8 weeks ($\pm$ 3 days) thereafter during the Treatment Continuation Period, and at the post-treatment follow-up visit to determine urine electrolytes (magnesium, phosphorus and calcium) and urine creatinine.
16. **Parathyroid Hormone (PTH):** Assessment of PTH will be performed if a Grade 2 or higher hypocalcemia or hypophosphatemia is reported.

17. **PK Blood Sampling: Day 14 (Enzalutamide Run-In Period):** Plasma samples for analysis of enzalutamide and N-desmethyl enzalutamide will be collected at pre-dose and 0.5, 1, 2, 3, 4, and 6 hrs post-dose on Day 14 of Enzalutamide Run-In Period, the day prior to administration of the first dose of combination study treatment (GSK2636771 and enzalutamide). **Week 5, Day 29 (Treatment Continuation Period):** Blood and plasma samples for analysis of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be collected at pre-dose and 0.5, 1, 2, 3, 4, and 6 hrs post-dose. Actual date and time of sample collection and dosing of study treatments must be recorded. Explanations are required for any deviations of more than 5 minutes from the planned time during the first 2 hrs and for deviations of more than 20 minutes from the planned time for samples collected at 3 hrs up to 6 hrs post-dose. **Week 8 and Week 12 (Treatment Continuation Period):** Blood and plasma samples for analysis of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be collected pre-dose only.
18. **Disease Assessments:** Disease assessments at Screening must be performed within 28 days prior to enrollment (Day 1 of the Enzalutamide Run-In Period), or within 35 days prior to enrollment (Day 1 of the Enzalutamide Run-In Period if disease assessment is performed by MRI, to identify target and non-target lesions.
19. **CT scan or MRI:** Scans should be performed at Screening, Week 8 and then every 8 weeks (±7 days) during the first 48 weeks of the Treatment Continuation Period and then every 12 weeks (±7 days) thereafter in the Treatment Continuation Period, and at the time of disease progression. All confirmatory scans are to be performed within 4 weeks (±3 days) of a CR or PR. If a subject discontinues treatment for reasons other than disease progression, disease assessments should continue every 3 months until disease progression, initiation of new anti-cancer treatment, subject withdrawal of consent, or death.
20. **Bone Scan:** A bone scan is required for all subjects at Screening. For subjects without bone disease at baseline, subsequent bone scans should be performed as clinically indicated. Subjects with bone metastases at baseline should have a bone scan performed at Week 12 and then every 12 weeks (±7 days) thereafter in the Treatment Continuation Period, or as clinically indicated, and at the time of disease progression**.** If a subject discontinues treatment for reasons other than disease progression, bone scans should continue every 3 months until disease progression, initiation of new anti-cancer treatment, subject withdrawal of consent, or death.
21. **CTC-Janssen:** Whole blood samples will be obtained at Screening; pre-dose on Day 1 (Week 1) and Day 22 (Week 4) of the Combination Treatment Period; pre-dose on Day 1 of Weeks 8, 16, 24 and 32 of the Treatment Continuation Period; and at time of disease progression.
22. **CTC-EPIC:** Whole blood samples will be obtained at Screening, pre-dose on Day 1 of Week 8 of the Treatment Continuation Period, and at the time of disease progression for protein and genomic analysis.
23. **Predictive Biomarkers Tumor Tissue:** For subjects enrolled into the study, additional slides of tumor tissue samples will be collected and submitted to the designated laboratory for analysis once a subject has received their first dose of GSK2636771 on Week 1, Day 1 of the Combination Treatment Period. Tumor tissue may be obtained from archived tissue samples or fresh tumor tissue submitted for the PTEN testing. If additional tumor tissue is not available, no new biopsy procedure is required for predictive biomarker analysis. Refer to the SRM for details about the number of slides to be submitted, preparation, handling and shipping.
24. **Tumor Biopsies for PD and progression**: These biopsies are optional and may be undertaken in select cases upon agreement with the investigator and when consent is provided by the subject. For pharmacodynamic biomarker analyses, fresh tissue biopsies would be collected between Day 12 of the Enzalutamide Run-in Period and Week 1/Day 1, prior to any treatment with GSK2636771, and 2-4 hours post dose between Days 8 and 15 of the Combination Treatment Period (post-treatment). For subjects who consent to the optional progression biopsy, a fresh tumor biopsy should be completed if the subject initially responded to combination treatment and then progressed.
25. **cfDNA/RNA/Soluble Markers:** Plasma samples will be obtained from collected blood samples at Screening, pre-dose on Weeks 1, 4, 8, 16, 24, and 32 of the Combination Treatment Period, and at the time of treatment discontinuation due to disease progression. Plasma will be analyzed for genomic changes in the circulating tumor DNA, RNA, and soluble markers.
26. **Genetic Research:** A 6-mL blood sample should be collected after Screening, preferably on Week 1, Day 1 of the Combination Treatment Period, if informed consent has been obtained for genetic research.
27. **Study Treatment:** Enzalutamide monotherapy should be taken once daily during the Enzalutamide Run-In Period. Enzalutimide will be self adiministered in the clinic on Day 14 of the Enzalutamide Run-In Period. GSK2636771 and enzalutamide will be administered in the clinic on Week 1, Day 1 of the Combination Treatment Period and on days when blood, plasma, and/or urine samples are collected for analysis of PK, CTC, and/or urine electrolytes.

28. **Post-Treatment Follow-Up Visit:** ***ONLY*** subjects who withdraw during the Enzalutamide Run-In Period or withdraw from study treatment ***due to*** disease **progression** (see Section 5.2) **should have a post-treatment follow-up visit conducted within approximately 30 days (-2/+7 days) of last dose of study treatment(s). If a subject is unable to** return to the clinic due to hospitalization, site staff is encouraged to call subject for assessment of AEs.
29. **Extended Follow-Up Visits:** Subjects who withdraw from study treatment ***without*** disease progression should be contacted every 3 months (±14 days) until disease progression, death, withdrawal of consent, or subject is lost to follow-up. Contact may include a clinic visit, a telephone contact, or an e-mail. The initiation of any new anti-cancer treatments and date of last contact should be documented.
30. **Post-Extended Follow-Up/EOS Visit:** ***ONLY*** subjects who discontinue the Extended Follow-Up Visits should have a Post-Extended Follow-Up/EOS Visit performed.
31. Subjects are not required to discontinue treatment on the basis of PSA progression alone or for the worsening of an isolated disease site that is not clinically significant (see Section 5.2).
32. When collected as part of the routine standard of care for a subject, LDH will be reported.
33. Complete clinical chemistries laboratory assessments at Week1/Day 1 and **again on either Day 3 or Day 4**. The Day 3 or Day 4 assessments can be completed at a local laboratory and does **not** require a clinic visit. The hematology panel does NOT need to be collected on Day 3/ Day.4. Review of these labs must occur before Week 2, Day 1 visit.
34. Includes assessments for 25-OH D and 1,25-OH2 D.
35. Includes urine and blood and/or serum samples. Must be collected at the same time of day (±1 hour) to eliminate diurnal effects, and after fasting. See SRM for additional details on the specific assessments and sample collection.

Table 16 Time and Events Table for Dose Expansion Phase

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**	**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression[31]**	**Post-Treatment Follow-Up Visit[28]**	**Extended Follow-Up Visits[29]**	**Post-Extended Follow-Up /EOS Visit[30]**
		Day -14 to Day -1	Day 1 to Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Week 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window				*+1 day*	*±1 day*	*±1 day*	*±1 day*	*±1 day*	*+5days Week 12 only; ±3 days for all other visits*	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Clinical Assessments													
Informed Consent	X[3]	X[4]											
Demographics	X												
Medical History		X											
Determination of PTEN Deficiency Status	M[5]												
Safety Assessments													
ECOG PS		X		X		X	X	X	Week 8 and then Q8wks	X	X		X
Physical Exam		X		X					Week 8 and then Q8wks		X		X
Height[8]		X											
Weight		X		X					Week 8 and then Q8wks		X		X
Vital Signs[9]		X		X	X	X	X	X	X		X		X
12-Lead ECG[10]		X[6]					X		Week 8 and then Q8wks		X		X
ECHO/MUGA		X[6,7]		As clinically indicated									
AE Monitoring			Continuous							X[11]	X[11]		

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**	**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression[31]**	**Post-Treatment Follow-Up Visit[28]**	**Extended Follow-Up Visits[29]**	**Post-Extended Follow-Up /EOS Visit[30]**
		Day -14 to Day -1	Day 1 to Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Week 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window				*+1 day*	*±1 day*	*±1 day*	*±1 day*	*±1 day*	*+5days Week 12 only; ±3 days for all other visits*	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Concomitant Medications		X	Continuous								X		
Laboratory Assessments[12]													
Hematology/ Clinical Chemistry		X[6]		X	X	X	X	X	X		X		X
Ionized Calcium		X[6]		X[33]	X	X	X	X	X		X		X
Vitamin D[34]		X[6]					X				X		X
Coagulation: PT, PTT, INR		X[6]		X			X						
Liver function Tests		X[6]		X	X	X	X	X	X		X		X
Urinalysis[13] Urine Microscopy[13] UPC[14]		X[6]		X			X		X		X		X
Urine Electrolytes[15]		X[6]		X[33]		X	X		Week 8 and then Q8wks		X		
Parathyroid Hormone				X	As clinically indicated[16]								
Bone Markers[35]				X				X	Weeks 12 and 24		X		X
PSA and LDH[32]		X[6]		X					X	X	X		X
Serum Testosterone		X[6]									X		X
PK Assessments													
PK Blood Sampling[17]								X	Weeks 8 and 12				

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**	**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression[31]**	**Post-Treatment Follow-Up Visit[28]**	**Extended Follow-Up Visits[29]**	**Post-Extended Follow-Up /EOS Visit[30]**
		Day -14 to Day -1	Day 1 to Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Week 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window				*+1 day*	*±1 day*	*±1 day*	*±1 day*	*±1 day*	*+5days Week 12 only; ±3 days for all other visits*	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Disease Assessments[18]													
CT scan or MRI[19]		X[6,7]							Week 8 and then Q8wks to Week 48; then Q12wks	X		X	
Chest X-ray or Chest CT scan		X[6,7]											
Bone Scan[20]		X[6,7]							Week 12 and then Q12wks	X		X	
Biomarker Assessments													
CTC – Janssen[21]		X		X			X		Weeks 8, 16, 24, and 32	X			
CTC – EPIC[22]		X							Week 8 only	X			
Predictive Biomarker: Tumor Tissue[23]				X									
Progression Tumor Biopsy[24]										X			
Tumor Biopsies for Pharmacodynamics[24]			X (Day 14)		X[24]								
cfDNA/RNA/Soluble Markers[25]		X		X			X		Weeks 8, 16, 24, and 32	X			

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**	**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression**[31]	**Post-Treatment Follow-Up Visit**[28]	**Extended Follow-Up Visits**[29]	**Post-Extended Follow-Up /EOS Visit**[30]
		Day -14 to Day -1	Day 1 to Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Week 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window				*+1 day*	*±1 day*	*±1 day*	*±1 day*	*±1 day*	*+5days Week 12 only; ±3 days for all other visits*	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Biomarker Assessments *continued*													
Blood Sample for Genetic Research[26]				X									
Study Treatments[27]													
Enzalutamide			Continuous	Continuous									
GSK2636771				Continuous									

Abbreviations: AE, adverse event; cfDNA, circulating-free tumor DNA; CT, computed tomography; CTC, circulating tumor cells; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOS, End of Study; HbA1C, hemoglobin A1C; INR, international normalization ratio; M, mandatory; MRI, magnetic resonance imaging; MUGA, multigated acquisition scan; O, optional; PD, pharmacodynamics; PK, pharmacokinetics; PS, performance status; PSA, prostate-specific antigen; PT, prothrombin time; PTEN, phosphatase and tensin homolog; PTH, parathyroid hormone; PTT, partial thromboplastin time; Q4wks, every 4 weeks; Q8wks, every 8 weeks; Q12wks, every 12 weeks; UPC, urine:protein:creatinine; Wk(s), week(s)

1. **Study Assessments:** All assessments may be performed more frequently if clinically appropriate. Assessments scheduled on days of dosing should be completed prior to the administration of study treatments, unless otherwise specified
2. **Study Assessments:** Assessments throughout the study are calendar based starting from Week 1, Day 1 of the Combination Treatment Period (the first dose of combination treatment). Dose interruptions should not alter the assessment schedule for any subsequent treatment period.
3. **Pre-Screening Informed Consent:** Separate pre-screening informed consent must be obtained prior to initiation of any pre-screening procedures or assessments.
4. **Screening Informed Consent:** Informed consent must be obtained prior to initiation of any screening procedures or assessments..
5. **PTEN Deficiency Status (Mandatory):** Tumor tissue samples (archived or fresh tumor tissue obtained by pre-treatment biopsy) will be collected to determine PTEN deficiency status of the tumor by the designated central laboratory. Refer to the SRM for details about the number of slides to be submitted, preparation, handling and shipping. Results of

the PTEN deficiency testing from the central laboratoryonly will be used to determine if the subject is eligible to continue Screening. Only subjects with PTEN deficient tumor based on central laboratorytesting results will be screened. **Any remaining tumor tissue may be used for other predictive biomarker analyses** if consent has been obtained.

6. **Screening:** When possible, screening assessments that require imaging, ECG, ECHO/MUGA, or laboratory studies should be performed AFTER PTEN status has been determined.
7. **Screening:** All screening assessments must be completed and all entry criteria must be met prior to assessments on Day 1 of Enzalutamide Run-In Period. EXCEPTION: ECHO/MUGA must be completed within 28 days of enrollment (Day 1 of Enzalutamide Run-In Period), and disease assessment must be completed within 28 days (35 days if MRI is used) prior to enrollment (Day 1 of the Enzalutamide Run-In Period).
8. **Height** is only measured at Screening**.**
9. **Vital Signs:** Blood pressure, temperature and heart rate will be measured. Vital signs may be measured more frequently if clinically warranted.
10. **ECG:** A single 12-lead ECG is to be performed ***before*** vital signs are measured and any blood draws, if assessments are planned at the same nominal time point.
11. **AE Monitoring:** Continued monitoring of AEs applies only to ongoing events at time of treatment discontinuation.
12. **Laboratory Assessments:** Refer to Section 8.6.6 (Table 17) for list of specific laboratory tests to be performed. Assessments may be performed within 24 hrs prior to scheduled visit (liver function tests and urine tests for UPC may be performed up to 72 hrs prior to a scheduled visit) to ensure availability of results.
13. **Urinalysis and Urine Microscopy:** Urinalysis and urine microscopy will be performed at the time points indicated. Assessments may be performed within 24 hrs prior to a scheduled visit to ensure availability of results.
14. **UPC:** Urine sample for UPC is to be collected at the time points indicated. Perform UPC with the first morning urine specimen (if possible) when urine dipstick protein ≥2+. Urine samples for UPC may be collected up to 72 hrs prior to a scheduled visit to ensure that results are available at time of visit. If the urine sample collected at Screening is contaminated with other bodily fluids, UPC will not be determined and subject will remain eligible for the study.
15. **Urine Electrolytes:** Urine samples will be obtained at Screening, pre-dose on Day 1 (Week 1), Day 3 OR Day 4, Day 15 (Week 3), Day 22 (Week 4) of the Combination Treatment Period, Week 8 and then every 8 weeks (± 3 days) thereafter during the Treatment Continuation Period, and at the post-treatment follow-up visit to determine urine electrolytes (magnesium, phosphorus and calcium) and urine creatinine.
16. **Parathyroid Hormone (PTH):** Assessment of PTH will be performed if a Grade 2 or higher hypocalcemia or hypophosphatemia is reported.
17. **PK Blood Sampling: Week 5, Day 29 (Treatment Continuation Period):** Blood and plasma samples for analysis of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be collected at pre-dose and 1, 2, and 3 hrs post-dose if a morning clinic visit is scheduled, or at approximately 5 to 6, 6 to 7, and 7 to 8 hrs post-dose if an afternoon clinic visit is scheduled. Actual date and time of sample collection and dosing of study treatments must be recorded. Explanations are required for any deviations of more than 5 minutes from the planned time during the first 2 hrs and for deviations of more than 20 minutes from the planned time for samples collected at 3 hrs up to 8 hrs post-dose. **Week 8 and Week 12 (Treatment Continuation Period):** Blood and plasma samples for analysis of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be collected pre-dose only.
18. **Disease Assessments:** Disease assessments at Screening must be performed within 28 days prior to enrollment (Day 1 of the Enzalutamide Run-In Period), or within 35 days prior to enrollment (Day 1 of the Enzalutamide Run-In Period if disease assessment is performed by MRI, to identify target and non-target lesions.
19. **CT scan or MRI:** Scans should be performed at Screening, Week 8 and then every 8 weeks (±7 days) during the first 48 weeks of the Treatment Continuation Period and then every 12 weeks (±7 days) thereafter in the Treatment Continuation Period, and at the time of disease progression. All confirmatory scans are to be performed within 4 weeks (±3 days) of a CR or PR. If a subject discontinues treatment for reasons other than disease progression, disease assessments should continue every 3 months until disease progression, initiation of new anti-cancer treatment, subject withdrawal of consent, or death.
20. **Bone Scan:** A bone scan is required for all subjects at Screening. For subjects without bone disease at baseline, subsequent bone scans should be performed as clinically indicated. Subjects with bone metastases at baseline should have a bone scan performed at Week 12 and then every 12 weeks (±7 days) thereafter in the Treatment

Continuation Period, or as clinically indicated, and at the time of disease progression**.** If a subject discontinues treatment for reasons other than disease progression, bone scans should continue every 3 months until disease progression, initiation of new anti-cancer treatment, subject withdrawal of consent, or death.

21. **CTC-Janssen:** Whole blood samples will be obtained at Screening; pre-dose on Day 1 (Week 1) and Day 22 (Week 4) of the Combination Treatment Period; pre-dose on Day 1 of Weeks 8, 16, 24 and 32 of the Treatment Continuation Period; and at time of disease progression.
22. **CTC-EPIC:** Whole blood samples will be obtained at Screening, pre-dose on Day 1 of Week 8 of the Treatment Continuation Period, and at the time of disease progression for protein and genomic analysis.
23. **Predictive Biomarkers Tumor Tissue:** For subjects enrolled into the study, additional slides of tumor tissue samples will be collected and submitted to the designated laboratory for analysis once a subject has received their first dose of GSK2636771 on Week 1, Day 1 of the Combination Treatment Period. Tumor tissue may be obtained from archived tissue samples or fresh tumor tissue submitted for the PTEN testing. If additional tumor tissue is not available, no new biopsy procedure is required for predictive biomarker analysis. Refer to the SRM for details about the number of slides to be submitted, preparation, handling and shipping.
24. **Tumor Biopsies for PD and progression**: These biopsies are optional and may be undertaken in select cases upon agreement with the investigator and when consent is provided by the subject. For pharmacodynamic biomarker analyses, fresh tissue biopsies would be collected between Day 12 of the Enzalutamide Run-in Period and Week 1/Day 1, prior to any treatment with GSK2636771, and 2-4 hours post dose between Days 8 and 15 of the Combination Treatment Period (post-treatment). For subjects who consent to the optional progression biopsy, a fresh tumor biopsy should be completed if the subject initially responded to combination treatment and then progressed..
25. **cfDNA/RNA/Soluble Markers:** Plasma samples will be obtained from collected blood samples at Screening, pre-dose on Weeks 1, 4, 8, 16, 24, and 32 of the Combination Treatment Period, and at the time of discontinuation of treatment due to disease progression. Plasma will be analyzed for genomic changes in the circulating tumor DNA, RNA, and soluble markers.
26. **Genetic Research:** A 6-mL blood sample should be collected after Screening, preferably on Week 1, Day 1 of the Combination Treatment Period, if informed consent has been obtained for genetic research.
27. **Study Treatment:** Enzalutamide monotherapy should be taken once daily during the Enzalutamide Run-In Period. Enzalutimide will be self adiministered in the clinic on Day 14 of the Enzalutamide Run-In Period. GSK2636771 and enzalutamide will be administered in the clinic on Week 1, Day 1 of the Combination Treatment Period and on days when blood, plasma, and/or urine samples are collected for analysis of PK, CTC, and/or urine electrolytes.
28. **Post-Treatment Follow-Up Visit:** ***ONLY*** subjects who withdraw during the Enzalutamide Run-In Period or withdraw from study treatment ***due to*** disease progression see Section 5.2) should have a post-treatment follow-up visit conducted within approximately 30 days (-2/+7 days) of last dose of study treatment(s). If a subject is unable to return to the clinic due to hospitalization, site staff is encouraged to call subject for assessment of AEs.
29. **Extended Follow-Up Visits:** Subjects who withdraw from study treatment ***without*** disease progression should be contacted every 3 months (±14 days) until disease progression, death, withdrawal of consent, or subject is lost to follow-up. Contact may include a clinic visit, a telephone contact, or an e-mail. The initiation of any new anti-cancer treatments and date of last contact should be documented.
30. **Post-Extended Follow-Up/EOS Visit:** ***ONLY*** subjects who discontinue the Extended Follow-Up Visits should have a Post-Extended Follow-Up/EOS Visit performed.
31. These assessments should be completed at the time of disease progression that leads to discontinuation of treatment. Subjects are not required to discontinue treatment on the basis of PSA progression alone or for the worsening of an isolated disease site that is not clinically significant (see Section 5.2).
32. When collected as part of the routine standard of care for a subject, LDH will be reported.
33. Complete clinical chemistries laboratory assessments at Week1/Day 1 and **again on either Day 3 or Day 4**. The Day 3 or Day 4 assessments can be completed at a local laboratory and does **not** require a clinic visit. The hematology panel does NOT need to be collected on Day 3/ Day.4. Review of these labs must occur before Week 2, Day 1 visit.
34. Includes assessments for 25-OH D and 1,25-OH2 D.
35. Includes urine and blood and/or serum samples. Must be collected at the same time of day (±1 hour) to eliminate diurnal effects, and after fasting. See SRM for additional details on the specific assessments and sample collection

8.2. Consent

A signed, written ICF must be obtained from the subject prior to any study-specific procedures or assessments.

Each subject will have adequate time to provide written informed consent of his or her own free will and prior to conducting any study procedures according to International Conference on Harmonization (ICH) and applicable local regulations and guidelines. Each subject will be provided a copy of their signed ICF prior to the initiation of any study procedures.

8.2.1. Consent for Pre-Screening

The subject will be asked to provide written informed consent for pre-screening prior to any of the pre-screening assessments outlined in the Time and Events Tables (Section 8.1) being performed.

8.2.2. Consent for Screening

If, during pre-screening, the subject is determined to have a PTEN deficient tumor, the subject will be asked to provide written informed consent prior to screening for enrollment in the study. The investigator or other designated study personnel will determine if the subject is eligible for enrollment in the study by reviewing the eligibility criteria and completing all of the Screening assessments outlined in the Time and Events Tables in Section 8.1.

8.3. Pre-Screening and Screening

8.3.1. Pre-Screening: Determination of PTEN Deficiency Status

A pre-screening assessment must be completed to determine the PTEN deficiency status of the subject's tumor.

After written informed consent is provided by the subject, archived tissue will be submitted to determine the PTEN deficiency status of the subject's tumor. If archival tumor tissue is not available, fresh tumor tissue should be obtained by a pre-treatment biopsy to determine PTEN deficiency. The PTEN testing will be performed at a GSK selected laboratory or laboratories and the tumor specimen should be provided to that laboratory or laboratories. The PTEN status will be communicated to sites by GSK authorized personnel.

If analysis of the archival tumor tissue specimen is not PTEN-deficient, fresh tumor tissue may be submitted to determine PTEN deficiency.

Details regarding pre-screening assessment and procedures with handling, processing and shipping tumor tissue samples are provided in the SRM.

8.3.2. Screening

Subjects with confirmed PTEN deficiency and have provide written informed consent for screening will be eligible to undergo specific screening assessments to determine eligibility for the study.

Screening assessments and procedures will be performed as indicated in the Time and Events Tables (Section 8.1). Screening assessments may be carried out over one or more days but should be completed within 14 days prior to the first planned dose of enzalutamide monotherapy (Day 1 of Enzalutamide Run-In Period), unless otherwise indicated.

Details regarding screening assessments and procedures are provided in the SRM.

8.4. Demographics and Medical History

Demographic data will include gender, year of birth, height, weight, ethnicity and geographic ancestry.

Medical, surgical, and treatment history including date of first diagnosis, histology, current sites of disease as well as cardiovascular risk factors, alcohol and tobacco history, plus family history will be taken as part of the medical history and disease status.

8.5. Critical Baseline Assessment

Cardiovascular medical history/risk factors will be assessed at baseline.

8.6. Safety

Measurements used to evaluate safety will include physical examinations, vital sign (BP, temperature and heart rate) measurements, ECOG performance status, 12-lead ECGs, ECHO/MUGA, clinical laboratory tests and monitoring for AEs. Planned time points for all safety assessments are listed in the applicable Time and Events Tables (Section 8.1).

Additional time points for safety tests (such as vital signs, physical examinations or laboratory tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

8.6.1. Physical Examination

A complete physical examination will be performed by a qualified physician according to local practices. At minimum, the examination should include assessments of the head and neck, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities. Complete physical examinations will be performed as indicated in the Time and Events Tables (Section 8.1) and as medically indicated throughout the study.

Height and weight will be measured and recorded as indicated in the Time and Event Tables (Section 8.1).

8.6.2. Vital Signs

Vital sign measurements will include BP, temperature, and heart rate. Vital signs may be measured as indicated in the Time and Event Tables (Section 8.1) or more frequently if warranted by clinical condition of the subject. Refer to the SRM for details regarding measurement of vital signs.

8.6.3. ECOG Performance Status

A subject's performance status will be assessed using the ECOG performance status scale (Appendix 1) as indicated in the Time and Events Tables (Section 8.1).

8.6.4. Electrocardiogram

Electrocardiograms (12-Lead ECGs) will be performed as indicated in the Time and Events Tables (Section 8.1) and obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

- At each assessment, a 12-lead ECG will be performed by qualified personnel at the site after the subject has rested at least 5 minutes in a semi-recumbent or supine position.
- If there are any clinically significant abnormalities including, but not limited to, QTcF >500 msec, confirm with two additional ECGs taken at least 5 minutes apart.
- Refer to Section 7.2.1 for QTc stopping criteria and additional QTc readings that may be necessary.
- Results of the ECG will be transmitted to a central storage facility. Any duplicate ECGs performed will be collected and evaluated, transmitted and stored in the same manner.

  Electrocardiograms (ECGs) may be centrally reviewed during the study on a post-hoc basis in response to any potential ECG safety concerns or at the end of the study. Any findings will be summarized and shared with study investigators but are not intended for individual subject safety management.

Refer to the SRM for further details on submission of ECGs.

8.6.5. Echocardiogram and/or Multi-gated Acquisition (MUGA) Scans

Echocardiograms (ECHOs) or MUGA scans will be performed at baseline to assess cardiac ejection fraction and cardiac valve morphology for the purpose of study eligibility, as specified in the Time and Events Tables (Section 8.1). Additional ECHO assessments may be performed if clinically warranted. The evaluation of the echocardiographer should include an evaluation for LVEF and both right and left-sided valvular lesions.

Copies of all ECHOs or MUGA scans performed on subjects who experience an absolute decrease >10% in LVEF compared to baseline concurrent with LVEF < institutional LLN may be required by GSK for review.

Refer to the SRM for further details on submission of ECHOs or MUGA scans.

8.6.6. Laboratory Assessments

Laboratory tests may be done up to 24 hrs prior to the scheduled visit. Laboratory test results are to be reviewed prior to the administration of study treatment.

Liver function tests and urine tests for UPC may be performed up to 72 hrs prior to the scheduled visit in order to have results available for review by investigator prior to the scheduled visit date.

Any laboratory test with a value outside the normal range may be repeated during Screening at the discretion of the investigator. A subject with a laboratory value outside the reference range(s) may be included only if the investigator and GSK Medical Monitor agree that it is unlikely to introduce additional risk factors and will not interfere with study procedures.

All laboratory tests with values that are significantly abnormal during participation in the study or within 30 days after the last dose of study treatments should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

If additional non-protocol-specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (i.e., AE, SAE or dose modification) the results must be recorded in the subject's eCRF.

All laboratory samples must be appropriately labelled and submitted with the applicable laboratory requisition form(s) according to central or local laboratory guidelines. Reference ranges will be provided to the site for each laboratory used by the site during the course of the study.

Refer to the SRM for details on the appropriate processing, handling and shipping of samples to avoid duplicate and/or additional blood draws.

Table 17 Clinical Laboratory Assessments

Hematology			
Platelet Count		*RBC Indices*:	*Automated WBC Differential:*
WBC Count (absolute)		MCV	Neutrophils
Hemoglobin		MCH	Lymphocytes
Hematocrit			Monocytes
			Eosinophils
Clinical Chemistry			
BUN	Potassium	AST	Total and direct bilirubin[1]
Creatinine	Chloride[2]	ALT	Uric Acid[2]
Glucose	Total CO_2	Alkaline phosphatase	Albumin
Sodium	Calcium	Lactate dehydrogenase[4]	Total Protein
Magnesium	Phosphate		
Urine Testing			
Urinalysis	Specific gravity pH, glucose, protein, blood and ketones by dipstick with microscopy (if clinically warranted or protein >1)		
UPC[3]			
Urine electrolytes	Urinary calcium, magnesium and phosphorus; urine creatinine from same urine specimen		
Other tests			
PSA			
Serum Testosterone			
Coagulation Tests: PT/PTT/INR			
Serum Parathyroid Hormone (PTH)			
Ionized Calcium			
25-OH D and 1,25-OH2 D			
Bone Markers[5]			

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; INR, international normalization ratio; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; PSA, prostate-specific antigen; PT, prothrombin time; PTH, parathyroid hormone; PTT, partial thromboplastin time; RBC, red blood cell; ULN, upper limit of normal; UPC, urine/protein/creatinine ratio; WBC, white blood cell

1. Direct bilirubin is required only if the total bilirubin is elevated (≥2 times ULN)
2. Chemistry evaluation of chloride or uric acid is not required where there are logistical constraints.
3. See Appendix 5.
4. For sites that routinely collect this information.
5. Refer to SRM

8.7. Pharmacokinetic Assessments

8.7.1. PK Assessments: Dose Escalation Phase

Plasma samples for PK analysis of enzalutamide and N-desmethyl enzalutamide will be collected from all subjects on Day 14 of the Enzalutamide Run-In Period. Blood and plasma samples for the analysis of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be collected from all subjects on Week 5, Day 29 and during Weeks 8 and 12 of the Treatment Continuation Period. These PK samples will be collected to evaluate if there is an effect of GSK2636771 on the PK of enzalutamide and to quantify the systemic exposure to GSK2636771, enzalutamide and N-desmethyl enzalutamide.

8.7.2. PK Assessments: Dose Expansion Phase

A reduced PK sampling strategy will be used for subjects in the Dose Expansion Phase (on Day 29 of Week 5). Pre-dose blood and plasma samples will also be collected on Day 1 of Weeks 8 and 12 of the Treatment Continuation Period) to quantify the systemic exposure to GSK2636771, enzalutamide and N-desmethyl enzalutamide.

8.7.3. PK Blood Sample Collection

Blood and/or plasma samples for PK analysis of GSK2636771 and/or enzalutamide and N-desmethyl enzalutamide will be collected at the time points indicated in the Time and Events Tables (see Section 8.1). Whenever possible, blood for PK samples should be drawn from the peripheral arm vein or from a central IV port. Each PK sample should be collected as close as possible to the planned time relative to the dose (i.e., time zero) administered to the subject on serial PK days. Once preliminary PK data have been reviewed, the planned sample collection times or study day may be revised based on newly available data (i.e., to obtain data closer to the time of peak plasma concentration) to ensure appropriate monitoring. These changes must be approved and documented by GSK, but will not constitute a protocol amendment.

For Dose Escalation Phase: Blood and/or plasma samples for analysis of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be collected according to a serial sampling scheme in the Dose Escalation Phase.

- **Day 14 (Enzalutamide Run-In Period);** the day prior to administration of the first dose of GSK2636771): Subjects will be instructed to fast overnight (at least 8 hrs) and withhold their dose of enzalutamide prior to the study visit on Day 14. Study treatments will be administered in the clinic after the pre-dose blood draw is completed. Subjects will continue to fast for 2 hrs post-dose. Plasma samples for analysis of enzalutamide and N-desmethyl enzalutamide will be collected at pre-dose and 0.5, 1, 2, 3, 4, and 6 hrs post-dose of enzalutamide (total of 7 samples).

- **Day 29, Week 5 (Treatment Continuation Period):** Subjects will be instructed to fast overnight (at least 8 hrs) and withhold the doses of study treatment prior to the study visit. Study treatments will be administered in the clinic after the pre-dose blood draws are completed. Subjects will continue to fast for 2 hrs post-dose. Blood and plasma samples for the analysis of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be collected at pre-dose and 0.5, 1, 2, 3, 4, and 6 hrs post-dose (total of 14 samples).

- **Weeks 8 and 12 (Treatment Continuation Period):** Subjects will be instructed to withhold the doses of study treatment prior to the study visit (no overnight fast is necessary). Study treatments will be administered in the clinic after the pre-dose blood draws are completed, either 1 hr before or 2 hrs after a meal. Blood and plasma samples for the analysis of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be collected pre-dose only (total of 2 samples per visit).

For Dose Expansion Phase: Blood and plasma samples for analysis of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be collected according to a sparse sampling scheme in the Dose Expansion Phase. Overnight fast is not necessary for any of these PK days. Study treatments should be administered either 1 hr before or 2 hrs after a meal.

- **Day 29, Week 5 (Treatment Continuation Period):**
    - Subjects scheduled for a *morning* clinic visit will be instructed to withhold the doses of study treatments prior to the study visit. Study treatments will be administered in the clinic after the pre-dose blood draws are completed (either 1 hr before or 2 hrs after a meal). Blood and plasma samples for analysis of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be collected at pre-dose and 1, 2, and 3 hrs post-dose (total of 8 samples).
    - Subjects scheduled for an *afternoon* clinic visit will take their doses of study treatments at the usual time in the morning (either 1 hr before or 2 hrs after a meal). Blood and plasma samples for analysis of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be collected approximately 5 to 6, 6 to 7, and 7 to 8 hrs post-dose (total of 6 samples).
- **Weeks 8 and 12 (Treatment Continuation Period):** Subjects will be instructed to withhold the doses of study treatment prior to the study visit. Study treatments will be administered in the clinic after the pre-dose blood draw is completed (either 1 hr before or 2 hrs after a meal). Blood and plasma samples for the analysis of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be collected pre-dose only (total of 2 samples per visit).

Details of PK blood and plasma sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the SRM.

8.7.3.1. Additional PK Blood Sample Collection

Blood and plasma samples for PK analysis will also be collected within 24-72 hrs after the last dose of study treatment(s) at the time of a treatment-emergent AE of special interest unless the event occurs on the same day that the Day 14 (Enzalutamide Run-In Period) and/or Week 5, Day 29 (Treatment Continuation Period) PK samples are obtained.

The date/time of the PK blood and plasma sample draw and the date/time of the last dose of study treatments prior to the PK blood and plasma sample draws will be recorded on the eCRF. If the date or time of the last dose of study treatment is unclear, provide the subject's best approximation. If the date/time of the last dose of study treatment cannot be approximated OR PK blood or plasma samples cannot be collected in the time period indicated above, do not obtain a PK samples. Refer to the SRM for instructions on sample handling and shipping of the PK samples.

8.7.4. Pharmacokinetic Sample Analysis

Blood and plasma analysis will be performed under the control of GSK Platform Technology and Science-Drug Metabolism and Pharmacokinetics (PTS-DMPK)/Scinovo, the details of which will be included in the SRM. Concentrations of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be determined in blood and plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once the blood and plasma has been analyzed for GSK2636771, enzalutamide and N-desmethyl enzalutamide any remaining blood or plasma may be analyzed for other compound-related metabolites and the results reported under a separate GSK PTS-DMPK protocol.

8.7.5. Meals, Alcohol, Tobacco and Activity Restrictions

Meals

Subjects will be instructed to take study treatments at least 1 hr before or 2 hrs after a meal unless otherwise instructed due to PK, CTC and/or urine electrolyte sampling (see Section 6.3 for details).

Alcohol

During each dosing session in which serial PK samples are collected, subjects will abstain from ingesting alcohol for 24 hrs prior to dosing until collection of the final PK sample.

Tobacco

Smoking while in the clinical unit will not be permitted. Subjects who use tobacco products may use nicotine patches while they are in the clinical unit.

Activity

All subjects will abstain from strenuous exercise for 48 hrs prior to each blood collection for PK and/or clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g., watch television, reading).

8.8. Clinical Activity

Refer to the Time and Events Tables (Section 8.1) for the schedule of disease assessments to be performed to assess the clinical activity of the combination therapy. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions or delays. For post-baseline assessments, a window of ±7 days is permitted to allow for flexible scheduling. Additional assessments may be performed as clinically indicated.

Refer to the SRM for further details on submission of CT scans, MRIs and bone scans.

8.8.1. Clinical Activity Endpoints

The secondary endpoint to evaluate the clinical activity of oral GSK2636771 + enzalutamide will be assessed using the disease progression endpoint (see Section 8.8.2.3) which differs from the disease progression criteria that lead to discontinuation of treatment (see Section 5.2). CTC response will also be determined and reported as an exploratory endpoint.

8.8.2. Disease Assessment

The primary endpoint is to evaluate the 12 week non-PD rate of oral GSK2636771 + enzalutamide according to PCWG2 guidelines (either by RECIST 1.1, PSA progression, and/or progression in bone). These assessments at Week 12 should occur at least 12 weeks (+5day window) after start of combination treatment.

For this study, the disease assessment will include the assessment of multiple parameters: RECIST 1.1 (see Appendix 4), PSA values per PCWG2 criteria (see Section 8.8.2.1), and radiographic response per PCGW2 criteria (see Section 8.8.2.2).

8.8.2.1. PSA Response per PCWG2 Criteria

Only subjects who have a baseline PSA value and at least one post-baseline assessment will be included in the analysis of PSA response.

PSA Response Rate is defined as proportion of subjects with a decrease of ≥50% in the PSA concentration from the baseline PSA value determined at least 12 weeks after start of treatment and confirmed after ≥4 weeks by an additional PSA evaluation.

PSA progression [Scher, 2008] is defined as:

- *If there has been a decline from baseline*: time from start of therapy to first PSA increase that is ≥25% and ≥2 ng/mL in absolute value from the nadir, and which is confirmed by a second value 3 or more weeks later (i.e., a confirmed rising trend) at least 12 weeks after the start of combination treatment
- *If there has NOT been a decline from baseline*: time from start of therapy to first PSA increase that is ≥25% and ≥2 ng/mL in absolute value from the baseline value, determined at least 12 weeks after start of combination treatment

8.8.2.2. Radiographic Response per PCWG2 Criteria

Bone progression [Scher, 2008] is defined as the appearance of ≥2 new lesions, and, for the first reassessment only, a confirmatory bone scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions. The first post-treatment bone scan (Week 12) will be used as the baseline scan with which all future bone scans are compared. The date of progression is the date of the first scan that shows a minimum of 2 additional new lesions. Subjects should not be discontinued from study treatment(s) due to the occurrence of bone scan changes in the first 12 weeks of combination treatment that do not meet PCWG2 guidelines for progression.

8.8.2.3. Disease Progression Endpoint

The disease progression endpoint is defined by 1 or more of the following criteria:

- PSA progression according to the PCWG2 criteria (Section 8.8.2.1) with accompanying progression by RECIST 1.1 or bone scan for subjects with measeurable baseline disease OR PSA progression if no measurable baseline disease
- Radiographic progression in soft tissue or bone by RECIST 1.1 for subjects with measurable disease
- Bone progression on bone scan according to the PCWG2 criteria (Section 8.8.2.2).

Subjects are not required to discontinue treatment on the basis of meeting PSA progression alone or for the worsening of an isolated disease site that is not clinically significant (see Section 5.2)

8.9. Translational Research

The analysis of biomarkers may depend on emerging pre-clinical and clinical biomarker data. All collected samples will be retained for a maximum of 15 years after the last subject completes the study. If subject withdraws consent for further treatment and data collection, all samples collected for the biomarker analysis at the time of withdrawal will still proceed for analysis to meet the intended objectives defined in this protocol. Details on sample collection, processing, storage and shipping procedures for all plasma samples are provided in the SRM.

8.9.1. Predictive Biomarkers

For subjects enrolled into the study, additional slides of tumor tissue samples will be collected and submitted to the designated central laboratory for analysis once a subject has received their first dose of GSK2636771 on Week 1, Day 1 of the Combination Treatment Period. The remaining tumor tissue submitted for the PTEN testing may be utilized for predictive biomarker analysis. If additional tumor tissue is not available, no newy biopsy procedure is required in order to obtain tumor tissue for predictive biomarker analysis.

Genetic changes known to alter or regulate PTEN function including mutation, loss of heterozygosity (LOH), silencing due to promoter methylation may be assessed. Additional proteins, DNA, RNA, or microRNA, related to activity of GSK2636771and enzalutamide or prostate cancer may also be analyzed. Any remaining tumor tissue may also be utilized to further develop a diagnostic assay.

Details on sample collection, processing, storage and shipping procedures are provided in the SRM.

8.9.2. Tumor Biopsies for PD and Disease Progression

If consent is provided by the subject, optional fresh tumor biopsies may be collected prior to combination treatment and 2 to 4 hours post dose on day 8 or 15 of combination treatment to understand target engagement and pharmacodyamic effects. It is preferable to repeat biopsy the same lesion to get a clearer picture of pre- and post-treatment effects. For subjects who initially responded to combination therapy and then progress, an optional progression tumor biopsy is requested in order to better understand the mechanism of resistance. It is preferable to obtain this biopsy from a new lesion or a lesion which had previously responded and then progressed. Biopsy samples from other lesions will be accepted as well. Both soft tissue and bone biopsies will be accepted.

Details on sample collection, processing, storage and shipping procedures for all samples are provided in the SRM.

8.9.3. Circulating Tumor Cells

Blood samples will be collected and analyzed to enumerate CTCs in circulation at the time points indicated in the Time and Events Tables (Section 8.1). The enumerated CTCs may also be utilized for additional analysis like alterations in AR or PTEN genes and may include additional genes implicated in the prostate cancer or related to AR/PI3K signalling pathway. If baselines CTCs are not observed in a subject, GSK may ask to terminate the further sampling for CTC enumeration in those subjects.

Additional blood samples will be collected at the time points indicated in the Time and Events Tables (Section 8.1) to isolate CTCs using an EPIC Sciences platform. The isolated CTCs will be analyzed for AR variants or other protein markers and potential genomic alterations (e.g., PTEN allele loss, AR amplifications, etc.).

If subject withdraws consent for further treatment and data collection, all samples collected for the biomarker analysis at the time of withdrawal will still proceed for analysis to meet the intended objectives defined in this protocol.

Details on sample collection, processing, storage and shipping procedures for all blood and tissue samples are provided in the SRM.

8.9.3.1. CTC Conversion Rate

CTC enumeration will be performed at a central laboratory using the analytically valid CellSearch system (Veridex LLC). For subjects with baseline CTC counts of ≥5 cells per 7.5 mL of blood, a conversion is defined as a decline in the CTC count to <5 cells per 7.5 mL of blood. Genetic analysis of CTCs may also be performed by other laboratories.

8.9.4. Circulating Cell Free DNA, RNA and Soluble Markers

Tumor-specific cfDNA levels detected in plasma or serum have been found to correlate with increasing tumor burden and decline following therapy. Furthermore, cfDNA in cancer subjects can harbor many genetic alterations (mutations, copy number changes, aberrant methylation), which are generally consistent with the tumor of origin. Thus, tumor-specific circulating cfDNA has the potential to be a useful biomarker of

therapeutic response as well as offering a less invasive blood based technique for identifying predictive biomarkers.

Plasma samples for analysis of cfDNA, RNA and soluble markers will be collected at the time points provided in the Time and Events Tables in Section 8.1.

If subject withdraws consent for further treatment and data collection, all samples collected for the biomarker analysis at the time of withdrawal will still proceed for analysis to meet the intended objectives defined in this protocol.

Details on sample collection, processing, storage and shipping procedures for all plasma samples are provided in the SRM.

8.10. Genetic Research

Information regarding genetic research is included in Appendix 7.

8.11. Exploratory Pharmacokinetic and Pharmacodynamic Analysis

Tumor size assessments, expressed as sum of longest diameters or the sum of the products of the two largest perpendicular diameters, described as a function of time using a 2-parameter model may be explored. Model parameters will be determined after administration of enzalutamide + GSK2636771.

The effect of GSK2636771 and enzalutamide on PSA levels also may be explored. Models including a linear model and a maximum effect model (Emax) may be fit to the change in PSA levels versus blood or plasma concentrations of GSK2636771, enzalutamide, and/or N-desmethyl enzalutamide.

This study will also include biopsies in subjects who consent to these optional procedures. Evaluation of pre and post treatment tumor tissue will be explored to determine pharmacodynamic effects. The mechanism of resistance to combination therapy will be explored in subjects who have progressed after initially responding to the combination therapy.

9. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE as outlined in Section 9.1 and Section 9.2, respectively.

9.1. Definition of an AE

An AE is any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally

associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits, abuse, or misuse.

Examples of events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or grade of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE).

"Lack of efficacy" or "failure of expected pharmacological action" *per se* is not to be reported as an AE or SAE. However, any signs and symptoms and/or clinical sequelae resulting from "lack of efficacy" will be reported as an AE or SAE, if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

9.2. Definition of an SAE

A serious adverse event (SAE) is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs.

If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. Protocol-Specific SAES:

- All events of possible study treatment-induced liver injury with hyperbilirubinemia defined as ALT ≥3 times ULN, and
- Bilirubin ≥2 times ULN (>35% direct) (or ALT ≥3 times ULN and INR >1.5 if INR is measured) or termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

  NOTE: Bilirubin fractionation should be performed if testing is available. If testing is not available, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥2 times ULN, then the event is still reported as a SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

- Any new primary cancer(s)

9.2.1. Sentinel Events

A Sentinel Event is a GSK-defined SAE that is not necessarily drug-related but has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. The GSK Medical Monitor is accountable for reviewing all SAEs for possible Sentinel Events which is mandated at GSK. The GSK Medical

Monitor may request additional clinical information on an urgent basis if a possible Sentinel Event is identified on SAE review. The current GSK-defined Sentinel Events are listed below:

- Acquired Long QT Syndrome
- Agranulocytosis/Severe Neutropenia
- Anaphylaxis & Anaphylactoid Reactions
- Hepatotoxicity
- Acute Renal Failure
- Seizure
- Stevens-Johnson Syndrome/Toxic Epidermal Necrosis

9.3. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) including those that worsen from baseline, and event felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an AE or SAE, in accordance with the definitions provided.

In addition, an associated AE or SAE is to be recorded for any laboratory test result or other safety assessment that led to an intervention, including permanent discontinuation of study treatment, dose reduction, and/or dose interruption/delay.

Any new primary cancer must be reported as an SAE.

Any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

9.3.1. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension

- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

This information should be recorded in the specific cardiovascular eCRF within 1 week of when the AE/SAE(s) are first reported.

9.3.2. Death Events

In addition, all deaths, whether or not they are considered SAEs, will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

This information should be recorded in the specific death eCRF within 1 week of when the death is first reported.

9.4. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression or hospitalization due to disease progression) does not need to be reported as an SAE.

Death due to disease under study is to be recorded on the Death eCRF form.

However, if the underlying disease (i.e., progression) is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with study treatment(s) or protocol design/procedures and the disease progression, then this must be reported as an SAE.

9.5. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the time the first dose of enzalutamide is administered on Day 1 of the Enzalutamide Run-In Period until 30 days following discontinuation of study treatments regardless of initiation of a new cancer therapy or transfer to hospice.

SAEs will be collected over the same time period as stated above for AEs. In addition, any SAE assessed **as related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment or GSK concomitant medication must be recorded from the time a subject consents to participate in the study

up to and including any follow-up contact. All SAEs will be reported to GSK within 24 hrs, as indicated in Section 9.5.2.

After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. At any time after 30 days the investigator may report any AE that they believe possibly related to study treatment.

9.5.1. Method of Detecting AEs and SAEs

Care must be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Examples of appropriate questions include:

"How are you feeling?"

"Have you had any (other) medical problems since your last visit/contact?"

"Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

9.5.2. Prompt Reporting of SAEs and Other Events to GSK

SAEs, pregnancies (in female partner of male subject), and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in the following table once the investigator determines the event meets the protocol definition for that event.

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hrs	SAE data collection tool	24 hrs	Updated SAE data collection tool
"Cardiovascular (CV) events" and/or "death"	Initial and follow-up reports to be completed within 1 week of when the CV event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow-up reports to be completed within 1 week of when the CV event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	2 Weeks	Pregnancy Notification Form	2 Weeks	Pregnancy Follow-up Form
Liver chemistry abnormalities:				
ALT ≥3 times ULN and bilirubin ≥2 times ULN (>35% direct) (or ALT ≥3 times ULN and INR >1.5, if INR is measured)[3]	24 hrs[1]	SAE data collection tool; Liver Event eCRF and liver imaging and/or biopsy eCRFs if applicable[2]	24 hrs	Updated SAE data collection tool. Updated Liver Event eCRF[2]
ALT ≥5 times ULN; ALT ≥3 times ULN with hepatitis or rash **or** 3 times ULN ≥4 weeks	24 hrs[1]	Liver Event eCRF[2]	24 hrs	Updated Liver Event eCRF[2]
ALT ≥3 times ULN and <5 times ULN and bilirubin <2 times ULN	24 hrs[1]	Liver Event eCRF does not need to be completed unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[2]		

Abbreviations: ALT, alanine aminotransferase; eCRF, electronic case report form; GSK, GlaxoSmithKline; hrs, hours; INR, international normalization ratio; SAE, serious adverse event; ULN, upper limit of normal

1. GSK to be notified at onset of liver chemistry elevations to discuss subject safety.
2. Liver Event Documents (i.e., "Liver Event eCRF" and "Liver Imaging eCRF" and/or "Liver Biopsy eCRF", as applicable) should be completed as soon as possible
3. INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.

Methods for detecting, recording, evaluating, and following up on AEs and SAEs are provided in the SRM.

9.5.3. Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

9.6. Reporting of Pregnancy

The investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to GSK as described below.

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

10. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

Subjects will be asked to provide a complete list of prescription and OTC medications that have been taken within 4 weeks prior to Screening. Subjects will be instructed to inform the investigator prior to starting any new medication(s), including herbal and OTC products, taken from the time of the first dose of enzalutamide monotherapy on Day 1 of the Enzalutamide Run-In Period until the end of the study (i.e., through the post-treatment follow-up visit). Any concomitant medication(s), including OTC and herbal product(s), taken during the study will be recorded in the eCRF. At a minimum, the drug name, dose and the dates of administration are to be recorded. Additionally, a complete list of all prior cancer therapies will be recorded in the eCRF.

Questions regarding concomitant medications should be directed to the GSK Medical Monitor for clarification.

If future changes to the list of permitted or prohibited medications are made as a result of emerging data, formal documentation will be provided to the investigative site by GSK. Any such changes will be communicated to the investigative sites in the form of a letter, which should be stored in the study file.

Recommended guidelines for the use of concomitant medication(s) with the combination of GSK2636771 with enzalutamide are provided in the following sections.

10.1. Permitted Medications

Supportive Care: Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, calcium supplements, Vitamin D supplements, and analgesics, and other care as deemed appropriate, and in accordance with local institutional guidelines.

Growth Factors and Bisphosphonates: The use of growth factors and bisphosphonates (if on a stable dose for at least 4 weeks) is permitted while participating in this study. However, the initiation of growth factors and bisphosphonates is not allowed during the first 4 weeks of study treatment.

Steroids: Use of steroids is discouraged while subject is undergoing treatment on this study. However, ***s***teroids (up to a maximum of 10 mg of prednisone or equivalent) are permitted provided that the subject has been on a stable dose for at least 4 weeks prior to enrollment.

Anticoagulants: Prophylactic doses of anticoagulants (i.e., heparin, warfarin) are permitted provided that the subject meets the prothrombin time (PTT)/International Normalization Ratio (INR) entry criteria (see Section 4.1.2) and INR is monitored in accordance with local institutional practice. Therapeutic doses of warfarin (defined as a dose resulting in INR >1.5) are prohibited within 14 days prior to first dose of enzalutamide monotherapy on Day 1 of the Enzalutamide Run-In Period through the post-treatment follow-up visit. Caution should be exercised if aspirin is used concomitantly with GSK2636771.

NSAIDs: Use of NSAIDs should be avoided during the study.

10.2. Prohibited Medications and Non-Drug Therapies

The following medications are prohibited within 28 days prior to the first dose of enzalutamide monotherapy (Day 1 of the Enzalutamide Run-In Period); unless otherwise stated) and while on treatment in this study:

- Any investigational drug(s)

- Other anti-cancer therapy (chemotherapy, radiation therapy, immunotherapy, biologic therapy, or hormone therapy other than for replacement).

  NOTE: If administration of medically indicated anti-cancer therapy is required while on study, prior approval from a GSK Medical Monitor must be obtained. Study treatment must be held while the anti-cancer therapy is administered. Re-starting of study treatment following the completion of anti-cancer therapy also requires prior approval of the GSK Medical Monitor.

- 5-alpha reductase inhibitors (e.g., finasteride, dutasteride)

- Androgens (e.g., testosterone, dihydroepiandrosterone)

- Herbal medication(s) that may affect PSA levels (e.g., saw palmetto)

- Other herbal medications including, but not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, yohimbe and ginseng.

10.2.1. Potential Drug Interactions with GSK2636771

10.2.1.1. GSK2636771 as Perpetrator of Drug-Drug Interactions

A preliminary study suggested the potential of CYP3A4 inhibition by GSK2636771; however, subsequent studies using human recombinant CYP3A4 and pooled human liver microsomes did not confirm this at concentrations tested (up to 100 μM). The preliminary study indicated GSK2636771 did not inhibit CYP1A2, 2C8, 2C9, 2C19 and 2D6 at up to 25 μM (10.8 μg/mL), the risk is low but was not fully discharged at higher concentrations. Medications that have a narrow therapeutic index and are substrates of CYP3A4 should be used with caution within 7 days or 5 half-lives (whichever is longer) prior to the first dose of GSK2636771 (Week 1, Day 1 of the Combination Treatment Period) and for the duration of study treatment through the post-treatment follow-up visit (Table 18). Medications that have a narrow therapeutic index and are substrates of CYP1A2, CYP2C8, 2C9 and 2C19, CYP2D6 and CYP2B6 should be used with caution. GSK2636771 did not inhibit transporters OATP1B1, OATP1B3, breast cancer resistance protein (BCRP) and p-glycoprotein (P-gp) up to 23-30 μM in vitro. Due to high GSK2636771 concentrations (up to 100 μM) observed in the FTIH study (P3B115717), there is a risk for renal transporter inhibition; however, in vitro data to discharge this risk is pending. Therefore, medications that are sensitive substrates of renal transporters OAT and OCT2 should be used with caution when administered with GSK2636771 (example drugs are listed in Table 18).

Table 18 Drugs Potentially Affected by GSK2636771: Use with Caution

Drugs/Agents	Therapeutic Area
CYP3A4 Substrates	
dihydroergotamine, ergonovine, ergotamine, methylergonovine	Ergot derivatives
Pimozide	Neuroleptic
bepridil, flecainide, lidocaine, mexilitine, amiodarone, quinidine, propafenone	Antiarrhythmics
tacrolimus, sirolimus	Immune modulators
quetiapine, risperidone, clozapine, atomoxetine	Miscellaneous
Antiplatelet agents	
ticlopidine, prasugrel or ticagrelor	Antiplatelet
Renal Transporter (OAT, OCT2) Substrates	
Methotrexate	Antineoplastic
dofetilde, pilsicainide, procainamide	Antiarrhythmic
Metformin	Antidiabetic

10.2.1.2. GSK2636771 as Victim of Drug-Drug Interactions

Pre-clinical and *in vitro* data suggested GSK2636771 is a substrate for UDP-glucuronosyltransferase (UGT) enzymes, while CYP enzymes do not appear to mediate the major metabolism pathways of GSK2636771. Therefore, drugs that are inhibitors and inducers of UGT enzymes should be used with caution (Table 19).

Effect on GSK2636771 exposure due to inhibition of transporters OATP1B1 and OATP1B3 is low due to the high permeability of GSK2636771.

Table 19 Drugs that may Potentially Affect GSK2636771: Use with Caution

Generic Drug Name	Therapeutic Area
Inducers of UGT enzymes	
rifamycin class agents (e.g., rifampin, rifabutin, rifapentine)	Antibiotics
carbamazepine, phenobarbital, phenytoin, s-mephenytoin	Antiepileptic drugs
Inhibitors of UGT enzymes	
Fluconazole	Antifungal
cisapride, probenecid, ranitidine, cyclosporine, diflunisal, sertraline, valproic acid, atavaquone, methadone, methsuximide, olanzapine, retigabine	Miscellaneous

Caution is also recommended when GSK2636771 and aspirin are used concomitantly.

10.2.2. Potential Drug Interactions with Enzalutamide

The following information is provided as an initial reference, however, please refer to the approved US FDA prescribing information [Xtandi, 2016] or the Xtandi Prescribing Information for the area where it is approved for the most current DDI information and contraindicated medications.

Drugs that Inhibit or Induce CYP3A4: Co-administration of enzalutamide with the strong CYP3A4 inhibitor itraconazole caused a slight increase (1.3-fold) in the composite AUC for enzalutamide plus N-desmethyl enzalutamide. Strong CYP3A4 inducers (e.g.,

carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, or rifapentine) are likely to reduce the plasma exposure of enzalutamide. Moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) and St. John's Wort may also reduce the plasma exposure of enzalutamide. Investigators should use clinical judgment as to whether or not to co-administer these agents.

Drugs that Inhibit or Induce CYP2C8: Co-administration of enzalutamide with a strong CYP2C8 inhibitor (e.g., gemfibrozil) increased the AUC of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold in healthy volunteers. Due to the potential for the change in enzalutamide exposure, co-administration with a strong CYP2C8 inhibitor is not recommended. If co-administration of enzalutamide cannot be avoided, reduce the dose of enzalutamide to 80 mg (2 capsules) once daily. If the administration of a strong CYP2C8 inhibitor is discontinued, the dose of enzalutamide should be increased to the previous dose level.

The effects of CYP2C8 inducers on the PK of enzalutamide have not been evaluated; therefore, co-administration of a strong or moderate CYP2C8 inducer (e.g., rifampin) should be avoided. Use of concomitant medication(s) with no or minimal CYP2C8 induction potential is recommended.

Effect of Enzalutamide on Drug Metabolizing Enzymes: Enzalutamide is a strong CYP3A4 inducer and a moderate inducer of CYP2C9 and CYP2C19 in humans and may lead to loss of efficacy of many commonly used medicinal products. Therefore, co-administration of enzalutamide with products with a narrow therapeutic range that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, pimozide, quinidine, sirolimus or tacrolimus), CYP2C9 (e.g., phenytoin, warfarin), and CYP2C19 (e.g., S-mephenytoin) should be avoided as enzalutamide may decrease the plasma exposure of these drugs. If enzalutamide is co-administered with an anticoagulant metabolized by CYP2C9 (such as warfarin or acenocoumarol) additional INR monitoring should be conducted.

Transporters: Concomitant use of enzalutamide with medicinal products that are sensitive substrates or transporters should generally be avoided if their therapeutic effect is of large importance to the subject, and if dose adjustments cannot easily be performed based on monitoring of efficacy or plasma concentrations.

Enzalutamide and N-desmethyl enzalutamide are potential inhibitors, but not substrates, of the efflux transporter P-gp. Enzalutamide may also be an inhibitor of BCRP, MRP2 and OAT3. Medicinal products with a narrow therapeutic range that are substrates for P-gp (e.g., colchicine, dabigatran etexilate, digoxin), BCRP, MRP2 or OAT3 (e.g., methotrexate) should be used with caution when administered concomitantly with enzalutamide and may require dose adjustment to maintain optimal plasma concentrations. Enzalutamide and its major metabolites are unlikely to inhibit the in vivo transport of OATP1B1, OATP1B3, OCT1, OCT2 or OAT1 substrates at clinically relevant concentrations.

11. LIFESTYLE RESTRICTIONS

11.1. Contraception Requirements

Male subjects with a female partner of childbearing potential or pregnant must agree to use two acceptable methods of contraception from time of Screening until 3 months after the last dose of study treatment. The two acceptable methods of contraception are:

1. Condom (as barrier method) is required, and
2. One of the following methods is also required:
    - Established use of oral, injected or implanted hormonal method by female partner
    - Use of intrauterine device or intrauterine system by female partner, or
    - Tubal ligation performed on female partner at least 6 months prior to the time of Screening of male subject
    - Use of additional barrier method including contraceptive sponge or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository)
    - Vasectomy or other surgical castration of male subject at least 6 months prior to the time of Screening of male subject

Abstinence: Male subjects may also elect abstinence, defined as sexual inactivity consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Complete abstinence from sexual intercourse must occur for 14 days prior to the first dose of enzalutamide monotherapy on Day 1 of the Enzalutamide Run-In Period, through the dosing period, and until 3 months after the last dose of study treatments.

Sperm Donation: Subjects must not donate sperm from the day of the first dose of enzalutamide monotherapy on Day 1 of the Enzalutamide Run-In Period through 3 months after the last dose of study treatments.

11.2. Other: Light Sensitivity and Allergens

During this study, subjects should be instructed to protect themselves against direct sun exposure and to avoid exposure to known allergens. Upon onset of any rash(es) during the study, subjects should be instructed to contact the investigator immediately and the rash management guidelines in Section 7.3.3 should be followed by investigators/sites.

11.3. Other: Hydration

Subjects are to be instructed to avoid dehydration while participating in the study. Subjects who have inadequate oral intake or who have difficulty maintaining hydration should discontinue treatment with GSK2636771 until adequate oral intake can be maintained. If the subject must discontinue treatment for more than 14 days due to inadequate oral intake, the subject should be withdrawn from the study.

12. DATA MANAGEMENT

For this study, data will be collected using a GSK defined eCRF, transmitted electronically to GSK and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSK Drug. Electronic CRF (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy.

When laboratory samples (i.e., hematology and clinical chemistry) are analyzed by a central laboratory the results will be stored in a database maintained by the central laboratory and transferred to GSK at agreed times.

In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

13. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

13.1. Hypotheses

13.1.1. Dose Escalation Phase

No formal statistical hypotheses will be tested. All analyses will be descriptive and exploratory.

13.1.2. Dose Expansion Phase

The hypothesized non-PD rate is provided in Section 13.2.2. In this case, a test that non-PD rate is less than or equal to the null hypothesis rate versus the non-PD rate is greater than or equal to the alternative rate is being performed using the stopping rules provided in Section 13.2.2. Descriptive statistics will be used to describe the response data at the dose(s) used in the expanded cohort(s).

13.2. Sample Size Determination

13.2.1. Dose Escalation Phase

The total number of subjects to be enrolled in the Dose Escalation Phase is not driven by statistical considerations, and will depend on the number of dose levels, number of subjects enrolled in each dose level, and the number of subjects enrolled at the recommended dose to evaluate long term safety. It is estimated that 24 subjects will be enrolled for the Dose Escalation Phase. The sample size of 24 subjects for the Dose Escalation Phase will provide the following 95% Clopper-Pearson confidence intervals (CI) for safety events as well as response data.

Safety Events	Frequency of Safety Events (95% CI)
1	4.2% (0.1% – 21.1%)
2	8.3% (1.0% - 27.0%)
3	12.5% (2.7% - 32.4%)
4	16.7% (4.7% - 37.4%)
8	33.3% (15.6% - 55.3%)
12	50.0% (29.1% - 70.9%)
16	66.7% (44.7% - 84.4%)
20	83.3% (62.6% – 95.3%)
21	87.5% (67.6% - 97.3%)
22	91.7% (73.0% - 99.0%)
23	95.8% (78.9% - 99.9%)

Abbreviation: CI, confidence interval

13.2.2. Dose Expansion Phase

An initial dose finding will be used to establish the MTD for the combination arm. Once the final dose is confirmed, at least 10 subjects will be enrolled at the appropriate dose level, using decision rules defined in Table 3. The sample size and stopping rules are based on the methodology of Lee [Lee, 2008].

Utilizing a null and alternative hypothesis of 5% and 30% respectively, a maximum of 20 subjects will be enrolled, with a minimum enrollment of 10 subjects. With an actual type I error rate (α) of 0.065 and 94.2% power, the design has stopping criteria defined for futility. The trial is designed to stop early for futility if the predictive probability of success is less than 6%. The type I error rate, power, and predictive probability of success to stop early for futility were derived from explicitly stating the minimum and maximum sample size, futility stopping rate, and selection of the optimizing criterion as the maximization of power under the alternative hypothesis. The Bayesian prior probability used in determining the design was Beta (0.10, 0.90), a distribution with a mean response rate (defined as lack of disease progression at 12 weeks according to PCWG2 criteria) of 10%. Under the null hypothesis, if the true response rate is 5%, the expected sample size of the design is 13.1 subjects and probability of early termination (PET) is 83.0%. Under the alternative hypothesis, if the true response rate is 30%, the expected sample size of the design is 19.7 subjects and PET is 4.3%.

However, the decision to terminate the Dose Expansion Phase will not depend solely on the results of the statistical methodology, but will take all factors into account. Additional subjects in a cohort may be enrolled even if the predictive probability suggests a low likelihood of activity in the Expansion Cohort (see Section 3.7.1).

13.3. Data Analysis Considerations

13.3.1. Analysis Populations

The All Treated Safety Population is defined as all subjects who receive at least one dose of GSK2636771 or Enzalutamide. Safety will be evaluated based on this analysis population.

The **All Treated Clinical Activity Population** is defined as all subjects who received at least one dose of GSK2636771. Clinical activity and evaluation of non-PD rate will be based on this analysis population. This will include subjects from both dose escalation and dose expansion.

The **All Evaluable Population** is defined as all subjects from All Treated Clinical Activity Population who have at least one post-dose disease assessment and have been exposed to study drug for at least 12 weeks or have progressed or have died or have withdrawn from the study for any reason. Dose Expansion futility analyses will be based on this population.

Pharmacokinetic (PK) Population: The PK Population will consist of all subjects from the All Treated Population for whom a PK sample is obtained and analyzed.

Additional analysis populations may be defined in the RAP.

13.3.2. Analysis Data Sets

The construction of analysis data sets will be performed in accordance with all applicable GSK standards and procedures.

13.3.3. Interim Analysis

13.3.3.1. Dose Escalation Phase

In the Dose Escalation Phase, available safety data will be reviewed and summarized on an ongoing basis. Review of preliminary safety data from all available dose cohorts will be performed in each study treatment combination before starting a new dose cohort and before selecting a dose level for expansion. Safety will be reviewed on an ongoing basis by the Safety Monitoring Team, composed of study investigators and key GSK personnel including the medical monitor, study manager, and study statistician.

13.3.3.2. Dose Expansion Phase

After the initial 10 subjects become evaluable at a dose level using a combination of dose escalation and dose expansion subjects, 12-week non-PD rate will be reviewed on an

ongoing basis and the number of responses observed will be compared with the stopping rules provided in Section 13.2.2.

13.3.4. Key Elements of Analysis Plan

Data will be listed and summarized according to the GSK reporting standards, where applicable. Complete details will be documented in the RAP. Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

As it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to provide valuable information, data from all participating centers will be pooled prior to analysis.

All data up to the time of study completion/withdrawal from study will be included in the analysis, regardless of duration of treatment.

As the duration of treatment for a given subject will depend on efficacy and tolerability, the duration of follow-up will vary between subjects. Consequently there will be no imputation for missing data.

Demographic and baseline characteristics will be summarized.

Summaries will generally be provided by cohort.

Details on the determination of tumor response are given in Appendix 4. Additional details on efficacy and safety analyses are provided in Section 13.3.4.1 and Section 13.3.4.2, respectively.

13.3.4.1. Efficacy Analyses

The All Treated Clinical Activity Population will be used for the analysis of efficacy data, and will be summarized separately for each dose level combining data from both dose escalation and does expansion. Efficacy analyses will be provided separately for each dose level.

Primary Analyses

The primary analysis is to determine whether the 12-week non PD rate is greater than or equal to 5%. The 12-week non PD rate is defined as the percentage of subjects without progression at Week 12. Progression is defined by RECIST 1.1 or progression in bone or PSA progression with accompanying progression by RECIST 1.1 or bone scan when baseline disease present or PSA progression solely if no other baseline disease. Subjects with unknown or missing response will not be treated as not having PD (i.e., subjects with NE will be included in the denominator when calculating the percentage of non-PD). Non-PD rate will be provided along with corresponding exact 95% CIs.

Secondary Analyses

PSA and RECIST 1.1 response data will be reported. Subjects with unknown or missing response data, including those who withdraw from the study without an assessment, will be treated as non-responders (i.e., they will be included in the denominator when calculating the percentage). No imputation will be performed for missing lesion assessment or tumor response data. An exact 95% CI will be computed for the PSA50 response rate and RECIST 1.1 confirmed response rate.

Further details about the efficacy analyses will be outlined in the RAP.

PSA Response Rate

PSA Response rate (RR) is defined as proportion of subjects with a decrease of ≥50% in the PSA concentration from the baseline PSA value determined at least 12 weeks after start of treatment and confirmed after ≥4 weeks by an additional PSA evaluation RR will be reported by dose level along with the exact 95% confidence interval. Waterfall plots will be presented that show the maximum percentage of change in PSA reduction from baseline.

Objective Response Rate

The objective response (ORR) rate is defined as the percentage of subjects with a confirmed complete response (CR) or a partial response (PR) at any time as per PCWG3-modified RECIST 1.1 (Appendix 5). Subjects with unknown or missing response will be treated as non-responders, i.e. these subjects will be included in the denominator when calculating the percentage. The number and types of responses, as outlined in PCWG3-modified RECIST 1.1, will be listed and summarized separately, as appropriate. The observed ORR, observed confirmed and unconfirmed ORR will be reported at the interim and final analysis for each cohort specified in treated dose, if data warrant. The estimates along with 95% exact confidence interval (CI) will be provided.

Radiographic Progression-free survival (rPFS) will be defined as the time from combination study treatment start until the first date of either disease progression or death due to any cause. The date of disease progression will be defined as the earliest date of disease progression as assessed by the investigator using RECIST version 1.1 or progression on bone scan. For subjects who have not progressed or died at the time of the rPFS analysis, censoring will be performed using the date of the last adequate disease assessment. In addition, subjects with an extended loss to follow-up or who start a new anti-cancer therapy prior to a rPFS event will be censored at the date of the last adequate disease assessment (e.g. assessment where visit level response is CR, PR, or stable disease [SD]) prior to the extended loss to follow-up or start of new anti-cancer therapy, respectively. Further details on rules for censoring will be provided in the RAP. rPFS will be summarized by dose level specified in expansion cohort using Kaplan-Meier quantile estimates along with 2-sided 95% CIs

Time to PSA progression

- *If there has been a decline from baseline*: time from start of combination treatment to **first** PSA increase that is ≥25% and ≥2 ng/mL in absolute value from the nadir, and which is confirmed by a second value 3 or more weeks later (i.e., a confirmed rising trend) at least 12 weeks after the start of treatment.

- *If there has NOT been a decline from baseline*: time from start of therapy to **first** PSA increase that is ≥25% and ≥2 ng/mL in absolute value from the baseline value, determined at least 12 weeks after start of treatment.

Time to PSA progression will be summarised using Kaplan-Meier methods by dose level.

Time to radiological progression will be defined as the time from combination study treatment start until the first radiological progression by RECIST 1.1 and/ or confirmed bone progression as defined in Section 8.8.2.2. Time to radiological progression will be summarised using Kaplan-Meier methods by dose level.

13.3.4.2. Safety Analyses

The All Treated Safety Population will be used for the analysis of safety data. All serially collected safety endpoints (e.g., laboratory tests, vital signs, ECGs) will be summarized according to the scheduled, nominal visit at which they were collected and across all on-treatment time points using a "worst-case" analysis. Complete details of the safety analyses will be provided in the RAP.

13.3.4.2.1. Extent of Exposure

The number of subjects administered study treatment will be summarized according to the duration of therapy. Details pertaining to dose interruptions or dose modification will also be listed.

13.3.4.2.2. Adverse Events

Adverse events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class. AEs will be graded by the investigator according to the CTCAE v4.0.

Events will be summarized by frequency and proportion of total subjects, by system organ class and preferred term. Separate summaries will be given for all AEs, treatment-related AEs, SAEs and AEs leading to discontinuation of study treatment. Adverse events (AEs), if listed in the CTCAE v4.0, will be summarized by the maximum grade. Otherwise, the AEs will be summarized by maximum intensity

Dose-limiting toxicities (DLTs) will be listed for each subject and summarized by dose cohort according to International Data Standards Library (IDSL) standards.

The incidence of deaths and the primary cause of death will be summarized.

13.3.4.2.3. Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized at each scheduled assessment according to CTCAE v4.0 grade. Laboratory data will also be summarized according to the subjects' baseline grade and maximum grade post-dose. The proportion of values lying outside the reference range will also be presented for laboratory tests that are not graded because there are no associated CTCAE 4.0 criteria. Summaries will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied).

Unscheduled data will be included in "overall" and "any post-screening" summaries which will capture a worst-case across all scheduled and unscheduled visits post first dose of study treatment. Further details are provided in the RAP.

13.3.4.2.4. Other Safety Measures

The results of scheduled assessments of vital signs, 12-lead ECG and ECOG performance status will be summarized. Summaries will include data from scheduled assessments only. All data will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied). All data will be listed. Further details are provided in the RAP.

13.3.4.3. Pharmacokinetic Analyses

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling and Simulation Department, GSK. Statistical analyses of the PK parameter data will be the responsibility of GSK Discovery Biometrics and Clinical Statistics.

Concentration-time data for GSK2636771, enzalutamide and N-desmethyl enzalutamide from the Dose Escalation Phase will be analyzed via standard non-compartmental methods. Parameters calculated include the area under the concentration-time curve from 0 to the last quantifiable blood or plasma concentration [AUC(0-t)] and/or over the dosing interval [AUC(0-τ)], Cmax, and Tmax, if data permit. Population PK parameters for GSK2636771 including oral clearance (CL/F), oral volume of distribution (V/F), and absorption rate constant (ka) will be estimated by pooling all data from this study with historical data, if data permit. Dependent on the final structural PK model, additional PK parameters may also be estimated. Sources of variability in PK parameters will be investigated during population modeling. Demographic parameters including, but not limited to age, sex, race, body weight, relevant laboratory parameters, will be evaluated as potential predictors of inter- and intra-subject variability for PK parameters. Population PK modeling will be performed using the non-linear mixed effects software NONMEM (Globomax LLC; Hanover, MD, US). Population PK of the active metabolite(s) may be characterized as appropriate.

Further details of the PK analyses will be described in the RAP.

13.3.4.4. Pharmacokinetic/Pharmacodynamic Analyses

Exploratory analyses will be performed to examine the relationship(s) between exposure (e.g., dose, plasma concentrations of GSK2636771, enzalutamide and N-desmethyl enzalutamide or other measure of exposure), and PD endpoints such as tumor size. Parameters describing the kinetics of tumor growth will be determined after administration of GSK2636771 + enzalutamide. Model parameters generated with data will be compared to investigate differences in the effect on tumor growth kinetics after administration of GSK2636771 + enzalutamide.

Pharmacokinetic/PD models also may be applied to describe the relationship between PK parameters and endpoints of clinical efficacy and safety (PSA and RECIST response rate, change from baseline in PSA, change from baseline in CTCs), as determined appropriate. Graphical analysis will be used initially to determine if there are any apparent

relationships between PK parameters and clinical endpoint. A simple linear model and Emax may be used to describe any apparent relationship(s). More complex models will be considered if appropriate.

Further details of PK/PD analyses will be described under a separate RAP. Results of the PK/PD analyses may be included in a report separate from the clinical study report (CSR).

13.3.4.5. Translational Research Analyses

All biomarker analyses will be conducted on the All Treated Population unless otherwise stated. Translational research analyses may include evaluation of PD indicators to explore the kinetics of tumor growth and molecular markers that may be predictive of clinical benefit.

Circulating tumor cells (CTC) may be evaluated for AR expression and other genomic markers that may be predictive of clinical benefit, as well as decreases in CTC from baseline.

Plasma collection at baseline, post-treatment and at time of disease progression will be used to analyze cfDNA, RNA and other soluble markers to understand clonal evolution, monitor response and explore predictive biomarkers. Archival or fresh biopy tissue may be utilized to identify potential predictive biomarkers (protein, DNA and RNA based markers). Optional PD and progression biopsies for subjects who have progressed from initially responding to the combination therapy may also be requested to understand pharmacodynamic effects and mechanism(s) of resistance.

Select biomarker data may be reported for all subjects consenting to pre-screening, based on the All Screened Population. Frequency of PTEN negative mCRPC subjects during pre-screening, as well as evidence of PTEN deletion, mutation, and promoter methylation, may be examined to further understand the mechanism of PTEN deficiency.

The results of these biomarker investigations may be reported separately from the main CSR. Analytic strategies for the final analysis of all biomarker data will be influenced by the data available (e.g., available material). Generally, all endpoints will be descriptively and/or graphically summarized but may be further determined at the completion of data collection.

14. STUDY CONDUCT CONSIDERATIONS

14.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

14.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, GSK will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- IRB/IEC review and favorable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments, e.g. genetic research described in Appendix 7, unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

14.3. Urgent Safety Measures

If an event occurs that is related to the conduct of the study or the development of the IP, and this new event is likely to affect the study of subjects, the Sponsor, and the investigator will take appropriate urgent safety measures to protect subjects against any immediate hazard.

The Sponsor will work with the investigator to ensure the IRB/IEC is notified.

14.4. Quality Control (Study Monitoring)

In accordance with applicable regulations, Good Clinical Practice (GCP), and GSK procedures, the site will be contacted prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the

discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents and to allocate their time and the time to their staff to monitor to discuss findings and any issues.

Monitoring visits will be conducted in a manner to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

14.5. Quality Assurance

To ensure compliance with ICH GCP and all applicable regulatory requirements, GSK may conduct quality assurance audits of the site. Regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

14.6. Study and Site Closure

The end of the study is defined as the date of the last visit of the last subject enrolled.

Upon completion or termination of the study, the monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, ICH GCP, and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

14.7. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

14.8. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The results summary will be posted to the Clinical Study Register no later than 8 months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit. When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing

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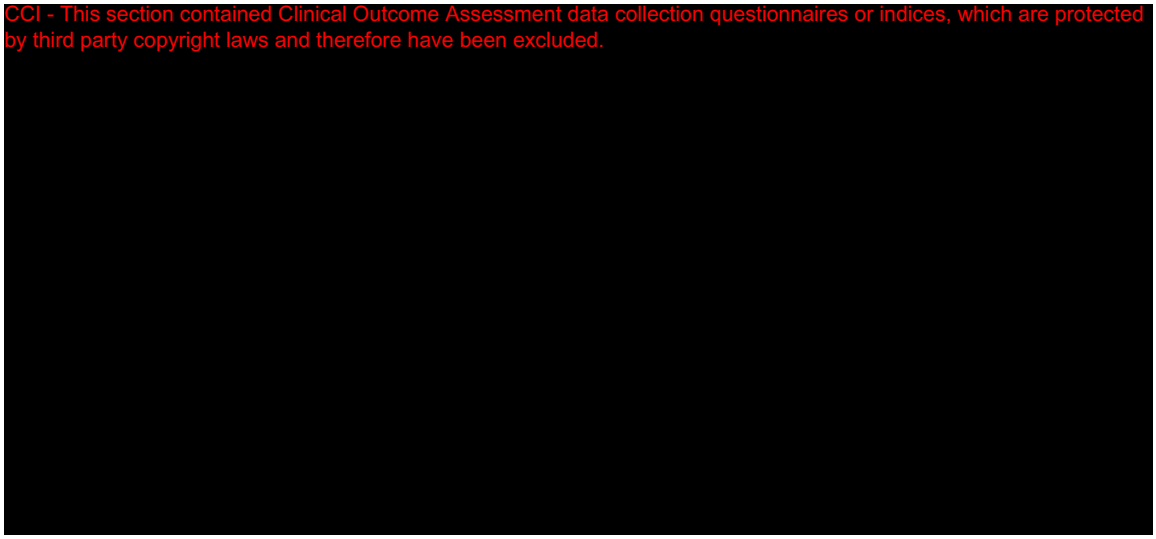
Xtandi (enzalutamide) Product Package Insert. Astellas Pharma US, Inc, Northbrook, IL and Medivation Inc., San Francisco, CA. October 2016.

Yoshimoto M, Joshua AM, Cunha IW, Coudry RA, Fonseca FP, Ludkovski O, Zielenska M, Soares FA, Squire JA. Absence of TMPRSS2:ERG fusions and PTEN losses in prostate cancer is associated with a favorable outcome. *Modern Pathol*. 2008;21:1451-1460.

16. APPENDICES

16.1. Appendix 1: ECOG Performance Status

Assessment of Eastern Cooperative Oncology Group (ECOG) performance status to evaluate daily living abilities is required at Screening as well as routinely throughout the treatment and at treatment discontinuation [Oken, 1982]:



Reference:

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649-655.

16.2. Appendix 2: NYHA Functional Classification System

The **New York Heart Association (NYHA) Functional Classification: Class I, II, III or IV Heart Failure [**NYHA, 1994**]** provides a simple way of classifying the extent of heart failure. It places subjects in one of 4 categories based on the level of limitation experienced during physical activity:

Class	Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Reference:

The Criteria Committee of the New York Heart Association (NYHA). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co. 1994:253–256.

16.3. Appendix 3: CKD-EPI equation

https://www.qxmd.com/calculate/egfr-using-ckd-epi.

16.4. Appendix 4: Disease Assessment per RECIST 1.1

Disease progression and response evaluations will be determined according to the definitions established in the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 [Eisenhauer, 2009].

Assessment Guidelines

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion. Contrast agents must be used in accordance with the Image Acquisition Guidelines.
- All measurements should be taken and recorded in millimeters (mm), using a ruler or calipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by computed tomography (CT) or magnetic resonance imaging (MRI) is required.

CT and MRI: Contrast enhanced CT with 5 mm contiguous slices is recommended. Minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimized for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible the same scanner should be used.

> **NOTE:** If CT contrast is contraindicated, acquire and submit a contrast-enhanced MRI of the abdomen/pelvis and an unenhanced CT of the chest in place of the enhanced CT for complete lesion assessment.

X-ray: In general, X-ray should not be used for target lesion measurements owing to poor lesion definition. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung; however, chest CT is preferred over chest X-ray.

Brain Scan: If brain scans are required, then contrast enhanced MRI is preferable to contrast enhanced CT.

Bone Scan (typically bone scintigraphy): Refer to Prostate Cancer Working Group 2 (PCWG2) guidelines.

Baseline Assessments

The following baseline disease (lesion) assessments must be performed within 28 days (or within 35 days if disease assessment is assessed by MRI) prior to first dose of enzalutamide (Day 1 of Enzalutamide Run-In Period) to identify target and non-target lesions:

- **CT/MRI:** A CT scan with contrast of the chest, abdomen, and/or pelvis, or other areas as indicated by the subject's underlying disease, is required for assessment of baseline disease burden.

  NOTE: Although CT scan is preferred, MRI may be used as an alternative method of baseline disease assessment for abdomen/pelvis, especially for those subjects where a CT scan is contraindicated due to allergy to contrast, provided that the method used to document baseline status is used consistently throughout study treatment to facilitate direct comparison. An unenhanced CT of the chest can replace the enhanced CT of the chest, but MRI of the chest is not recommended.

- **Bone Scan:** A baseline bone scan is required for all subjects. For subjects without bone disease at baseline, subsequent bone scans should only be performed as clinically indicated (e.g., presentation of bone pain). For subjects with bone disease at baseline, a bone scan is required every 12 weeks or as clinically indicated. In addition, in order to confirm a complete response (CR) in a subject with bone disease at baseline, a bone scan must be performed 1 week prior to the first set of images showing CR to 4 weeks after the next protocol specified assessment.

For subjects with palpable/superficial lesions, clinical disease assessments by physical examination should be performed at baseline and throughout study treatment as clinically indicated.

Confirmation of CR and partial response (PR) are required per protocol. Confirmation assessments must be performed no less than 4 weeks (±3 days) after the criteria for response have initially been met and may be performed at the next protocol scheduled assessment. If a confirmation assessment is performed prior to the next protocol schedule assessment, the next protocol scheduled evaluation is still required (e.g., evaluations must occur at each protocol scheduled time point regardless of unscheduled assessments).

Baseline documentation of target and non-target lesions

- All baseline lesion assessments must be performed within 28 days (or within 35 days if disease assessment is assessed by MRI) prior to the first dose of enzalutamide (Day 1 of the Enzalutamide Run-In Period).
- Lymph nodes that have a short axis of <10 mm are considered non-pathological and should not be recorded or followed.
- Pathological lymph nodes with <15 mm and but ≥10 mm short axis are considered non-measurable.
- Pathological lymph nodes with ≥15 mm short axis are considered measurable and can be selected as target lesions; however, lymph nodes should not be selected as target lesions when other suitable target lesions are available.
- Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and

recorded and measured at baseline. These lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

Note: Cystic lesions thought to represent cystic metastases should not be selected as target lesions when other suitable target lesions are available.

Note: Measurable lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered measurable. Bone scans, fluorodeoxyglucose-positron emission tomography (FDG-PET) scans or X-rays are not considered adequate imaging techniques to measure bone lesions.
- All other lesions (or sites of disease) should be identified as non-target and should also be recorded at baseline. Non-target lesions will be group by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Post-Baseline Assessments

For all subjects, post-baseline assessment should evaluate disease sites identified by baseline scans. Post-baseline disease assessment (CT scan or MRI) is required every 8 weeks (±7 days) during the first 48 weeks of treatment and then every 12 weeks (±7 days) thereafter or as clinically indicated.

For subjects with no bone disease at baseline, subsequent bone scans should only be performed as clinically indicated (e.g., presentation of bone pain).

For subjects with bone disease at baseline, a bone scan is required every 12 weeks (±7 days) or as clinically indicated.

Follow-up Assessments for Subjects Permanently Discontinued from Study Treatment

Refer to Section 5.2 (Permanent Discontinuation from Study Treatment) and the Time and Events Tables (see Section 8.1) for follow-up assessment of subjects who are to be followed for disease progression after permanently discontinuing from study treatment.

Assessment of Subject Completion

If the last radiographic assessment was more than 4 weeks prior to withdrawal from study and progressive disease has not been documented, a disease assessment should be obtained at the time of withdrawal from study.

Guidelines for Evaluation of Disease

Measurable and Non-measurable Definitions

Measurable lesion:

A non-nodal lesion that can be accurately measured in at least one dimension (longest dimension) of

- ≥10 mm with MRI or CT when the scan slice thickness is no greater than 5 mm. If the slice thickness is greater than 5 mm, the minimum size of a measurable lesion must be at least double the slice thickness (e.g., if the slice thickness is 10 mm, a measurable lesion must be ≥20 mm).
- ≥10 mm caliper/ruler measurement by clinical exam or medical photography.
- ≥20 mm by chest x-ray.

Additionally lymph nodes can be considered pathologically enlarged and measurable if:

- ≥15 mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5 mm). At baseline and follow-up, only the short axis will be measured.

Non-measurable lesion:

All other lesions including lesions too small to be considered measurable (longest diameter <10 mm or pathological lymph nodes with ≥10 mm and <15 mm short axis) as well as truly non-measurable lesions, which include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Measurable disease: The presence of at least one measurable lesion. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion.

Non-Measurable only disease: The presence of only non-measurable lesions.

Response Criteria

Evaluation of target lesions

Definitions for assessment of response for target lesion(s) are as follows:

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes must be <10mm in the short axis.
- **Partial Response (PR):** At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (e.g., percent change from baseline).

- **Stable Disease (SD)**: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
- **Progressive Disease (PD):** At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 mm.
- **Not Applicable (NA**): No target lesions at baseline.
- **Not Evaluable (NE):** Cannot be classified by one of the five preceding definitions.

Note:

- If lymph nodes are documented as target lesions the short axis is added into the sum of the diameters (e.g., sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis <10 mm) they should still have a measurement reported in order not to overstate progression.
- If at a given assessment time point all target lesions identified at baseline are not assessed, sum of the diameters cannot be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.
- All lesions (nodal and non-nodal) should have their measurements recorded even when very small (e.g., 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.
- If a lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

Evaluation of non-target lesions

Definitions for assessment of response for non-target lesions are as follows:

- **Complete Response (CR):** The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (e.g., <10 mm short axis).
- **Non-CR/Non-PD:** The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline ≥10 mm short axis.
- **Progressive Disease (PD)**: Unequivocal progression of existing non-target lesions.

- **Not Applicable (NA):** No non-target lesions at baseline.
- **Not Evaluable (NE):** Cannot be classified by one of the four preceding definitions.

Note:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- Sites of non-target lesions, which are not assessed at a particular time point based on the assessment schedule, should be excluded from the response determination (e.g., non-target response does not have to be "Not Evaluable").

New Lesions

New malignancies denoting disease progression must be unequivocal. Lesions identified in follow-up in an anatomical location not scanned at baseline are considered new lesions.

Any equivocal new lesions should continue to be followed. Treatment can continue at the discretion of the investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

Evaluation of Overall Response

The table below presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for subjects with measurable disease at baseline.

Evaluation of Overall Response for Subjects with Measurable Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-PD or NA or NE	No	PR
SD	Non-PD or NA or NE	No	SD
NE	Non-PD or NA or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR, complete response, PR, partial response, SD, stable disease, PD, progressive disease, NA, Not applicable; NE, Not Evaluable

Note:

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status

is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.

- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence and will be determined programmatically by GSK based on the investigators assessment of response at each time point.

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after first dose at a minimum interval of 56 days
- If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PD. Alternatively, subjects lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

Confirmation Criteria:

To be assigned a status of PR or CR, a confirmatory disease assessment should be performed no less than 4 weeks (±3 days) after the criteria for response are first met.

Confirmation of Response per RECIST 1.1

Confirmation of CR and PR are required per protocol. Confirmation assessments must be performed at least 4 weeks (±3 days) after the criteria for response have initially been met and may be performed at the next protocol scheduled assessment. If a confirmation assessment is performed prior to the next protocol-specified assessment, the next protocol-specified evaluation is still required (e.g., evaluations must occur at each protocol scheduled time point regardless of unscheduled assessments).

Bone disease: To confirm a CR in a subject with bone disease at baseline, a bone scan that was obtained before the response assessment indicating a CR must have been obtained no earlier than 1 week prior to that response assessment scan. Alternatively, a bone scan performed after a response assessment scan suggesting a CR must be done no more than 4 weeks after the next protocol specified assessment in order to confirm a CR.

Brain metastases: To confirm a CR in a solid tumor subject with brain metastases at baseline, brain imaging that is obtained before the response assessment indicating a CR must have been obtained no earlier than 1 week prior to that response assessment imaging. Alternatively, brain imaging performed after a response assessment imaging suggesting a CR in a solid tumor subject with brain metastases must be done no more than 4 weeks (±3 days) after the next protocol specified assessment in order to confirm a CR.

Reference:

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: Revised RECIST guidelines (version 1.1). *European Journal of Cancer*. 2009;45:228-247.

16.5. Appendix 5: Urine Protein Creatinine (UPC) Ratio

Clinical meaning of UPC

There is a good correlation between the ratio of protein concentration to creatinine concentration in a random urine sample and the amount of protein excreted over 24 hrs. Creatinine excretion is fairly constant throughout the day regardless of changes in urine flow rate.

Normal protein excretion is <150 mg/24 hrs and is similar for men and women.

Men excrete 20 mg to 25 mg of creatinine/kg of body weight/day.

Women excrete 15 mg to 20 mg of creatinine/kg of body weight/day.

Calculating UPC

UPC ratio = Urine protein (mg/dL) / Urine creatinine (mg/dL).

UPC ratio ≈ equivalent to grams of protein excreted in urine over 24 hrs.

Example: Subject has a urine protein = 90 mg/dL and urine creatinine = 30 mg/dL.

UPC ratio= (90 mg/dL) / (30 mg/dL) = 3

The calculated UPC ratio is 3, which correlates to roughly 3 g protein excretion in a 24-hr period.

Units for UPC ratio

Note: To calculate UPC, protein and creatinine concentrations must be expressed in the same units (mg/dL, g/L, or µmol/L). If, for example, protein concentration is expressed in mg/dL and creatinine concentration is expressed in µmol/L, conversion of one of the concentration values is required. Conversion factors are:

From	To	Conversion Factor
Conventional Units: mg/dL	SI Units: µmol/L	Multiply by 88.4
SI Units: µmol/L	Conventional Units: mg/dL	Divide 88.4

References:

NKF: NKF KDOQI Guidelines [Internet]. National Kidney Foundation; nd. KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Available from http://www.kidney.org/professionals/KDOQI/guidelines_ckd/p5_lab_g5.htm

Xin G, Wang M, Jian L, Xu F, Wang H. Protein-to-creatinine ratio in spot urine samples as a predictor of quantitation of proteinuria 2004. Clinica Chimica Acta 350:35-39.

16.6. Appendix 6: Liver Safety Drug Restart/Rechallenge Guidelines

If subject meets liver chemistry stopping criteria do not restart/rechallenge subject with study treatment unless:

- GlaxoSmithKline (GSK) Medical Governance approval **is granted** (as described below),
- Independent ethics committee (IEC) and/or institutional review board (IRB) approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

If GSK Medical Governance approval to restart/rechallenge subject with study treatment **is not granted**, then subject must permanently discontinue study treatment and may continue in the study for protocol-specified follow-up assessments.

1. Rechallenge Following Liver Stopping Events that are Possibly Related to Study Treatment

Following drug-induced liver injury (DILI), **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies** [Andrade, 2009]. Clinical outcomes vary by drug, with nearly 50% fatality with halothane re-administered within 1 month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

- Hypersensitivity[Andrade, 2009] with initial liver injury (e.g., fever, rash, eosinophilia)
- jaundice or bilirubin >2 x upper limit of normal (ULN) with initial liver injury (direct bilirubin >35% of total)
- subject currently exhibits severe liver injury defined by: alanine aminotransferase (ALT) ≥3 x ULN, bilirubin ≥2 x ULN (direct bilirubin >35% of total), or international normalization ratio (INR)>1.5
- serious adverse event or fatality has previously been observed with rechallenge of the drug [Papay, 2009; Hunt, 2010]
- evidence of treatment-related preclinical liability (e.g., reactive metabolites; mitochondrial impairment) [Hunt, 2010]

Rechallenge refers to resuming study treatment following DILI. Because of the risks associated with rechallenge after DILI this should only be considered for a subject for whom there is compelling evidence of benefit from a critical or life-saving medicine, there is no alternative approved medicine available, and a benefit:risk assessment of rechallenge is considered to be favorable.

Approval by GSK for rechallenge with study treatment can be considered where:

- Investigator requests consideration of rechallenge with study treatment for a subject who is receiving compelling benefit with study treatment that exceeds risk, and no effective alternative therapy is available.
- IEC or IRB approval for rechallenge with study treatment must be obtained, as required.
- If the rechallenge is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the rechallenge with study treatment. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for rechallenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If after study treatment rechallenge, subject meets protocol-defined liver chemistry stopping criteria, study treatment should be permanently discontinued.
- GSK Medical Monitor, and the IEC or IRB as required, must be informed of the subject's outcome following study treatment rechallenge.
- GSK to be notified of any adverse events, as per Section 9.

2. Restart Following Transient Resolving Liver Stopping Events NOT Related to Study Treatment

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g., biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with human leukocyte antigen (HLA) markers of liver injury.

Approval by GSK for study treatment restart can be considered where:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Restart risk factors (e.g., fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis), possible study treatment-induced liver injury or study treatment has an

HLA genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded

- IEC or IRB approval of study treatment restart must be obtained, as required.
- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- GSK Medical Monitor, and the IEC or IRB as required, must be informed of the subject's outcome following study treatment restart.
- GSK to be notified of any adverse events, as per Section 9 of the protocol.

REFERENCES:

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. *Expert Opin Drug Saf*. 2009;8:709-714.

Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. *Hepatol*. 2010;52:2216-2222.

Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, Hunt CM. Drug-induced liver injury following positive drug rechallenge. *Regul Tox Pharm*. 2009;54:84-90.

16.7. Appendix 7: Genetic Research

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including any treatment regimens under investigation in this study or any concomitant medicines;
- Cancer susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6-mL blood sample will be taken for deoxyribonucleic acid (DNA) extraction. A blood sample is collected at the baseline visit (Day 1 preferably for this study), after the subject has been randomized and provided informed consent for genetic research. If a subject initially declines to participate in genetic research and then changes their mind, a sample should be obtained at the earliest opportunity. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GlaxoSmithKline (GSK) may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the clinical study. Genetic informed consent must be obtained prior to any blood being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should

instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

16.8. Appendix 8: Country Specific Requirements

United Kingdom (UK): The UK Specific QTc Stopping Criteria should be applied to subjects enrolled in this study in the UK.

In line with local requirements, a subject enrolled and participating in this study in the UK that meets the criteria QTc[1] below will have study treatment withheld:

QTcB >500 msec

[1]Based on average QTc value of triplicate ECGs to include manual overread. For example, if an ECG demonstrates a prolonged QT interval, obtain two more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine whether the subjects should have study treatment withheld.

If the QTc prolongation resolves to Grade 1 or baseline, the subject may be re-started on the study treatment if the investigator and GSK Medical Monitor agree that the subject will benefit from further treatment.

Abbreviations: ECG, electrocardiogram; GSK, GlaxoSmithKline; QTc, corrected QT interval; QTcB, corrected QT interval by Bazett's formula; UK, United Kingdom

16.9. Appendix 9: Protocol Amendment Changes

16.9.1. Protocol Changes for Amendment 1 (08-Sep-2014) from Original Protocol (22-May-2014)

Where the Amendment Applies

This amendment applies to all sites and countries.

Summary of Amendment Changes with Rationale

Amendment 1 incorporates changes to Section 5.2, Permanent Discontinuation of Study Treatment(s) for clarification as requested by the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom.

List of Specific Changes

Section 5.2, Permanent Discontinuation of Study Treatment(s)

REVISED TEXT

Subjects may receive study treatment until disease progression, unacceptable toxicity, including meeting stopping criteria for liver chemistry as defined in Section 7.2.2, or death. Study treatment(s) ~~may~~**will** be permanently discontinued for any of the following reasons:

- Disease progression
- Death
- Unacceptable AE (including meeting liver chemistry stopping criteria as defined in Section 7.2.2)
- **Substantial** protocol deviation(s)

16.9.2. Protocol Changes for Amendment 2 (26-Feb-2015) from Protocol Amendment 1 (08-Sep-2014)

Where the Amendment Applies

This amendment applies to all sites and countries.

Summary of Amendment Changes with Rationale

Amendment 2 incorporates changes to list of authors and primary medical monitor (contact information) due to changes in personnel assignment within GSK; list of abbreviations was revised appropriately based upon addition/deletion of abbreviated terms used throughout the protocol; Time and Events Tables were revised for clarification of assessments and procedures to be performed and to reflect changes made throughout the body of the protocol.

List of Specific Changes

Sponsor Medical Monitor Contact Information

Role	Name	Day Time Phone Number	After-hours Phone/ Cell/ Pager Number	Fax Number	GSK Address
Primary Medical Monitor	PPD **MD, PhD**	PPD	PPD	PPD	**GlaxoSmithKline 1250 S. Collegeville Road Collegeville, PA 19426, USA** PPD
~~**Secondary Medical Monitor**~~	PPD ~~MD, PhD~~	PPD	PPD	PPD	~~GlaxoSmithKline 1250 S. Collegeville Road Collegeville, PA 19426, USA~~ PPD

Section 1.2.1 Clinical Safety, Pharmacokinetic Data and Clinical Activity of GSK2636771, first paragraph

REVISED TEXT

This study is ongoing; ~~and, as of February 2014, 53 subjects have been enrolled.~~ **the last subject was enrolled on 21-Aug-2014 for a total of 62 subjects.**

Section 1.3.1 Clinical Safety, Pharmacokinetic Data, and Clinical Activity of Enzalutamide

REVISED TEXT

Pharmacokinetics. Oral absorption of enzalutamide is rapid and independent of dose with Cmax achieved 1 to 2 hrs post-dose. It is 97 to 98% bound to plasma proteins, primarily albumin. N-desmethyl enzalutamide is 95 to 97% bound to plasma proteins. Enzalutamide is metabolized by CYP3A4 and CYP2C8 to an active metabolite N-desmethyl enzalutamide and primarily eliminated by hepatic metabolism (CYP3A4 and CYP2C8). The mean t1/2 is 5.8 days in patients. With daily administration, steady state is reached after approximately 30 days. **In order to achieve near-steady state enzalutamide exposure, a 14-day run-in period has been included in the study design (Section 1.5.3, and Section 3).** Enzalutamide accumulates approximately 8.3-fold relative to a single dose with a mean peak-to-trough ratio of 1.25. A high-fat meal did not alter the area under the concentration-time curve (AUC) of enzalutamide or its active metabolite, N-desmethyl enzalutamide.

Section 1.4.1.4 Risk of Drug-Drug Interaction (NEW SECTION)

NEW TEXT

The risk for GSK2636771 to affect enzalutamide via enzymes of CYP3A4 and CYP2C8 is low but not fully discharged. It is unknown if enzalutamide could potentially affect the exposure of GSK2636771 via UGT inhibition or induction, while the drug-drug interaction (DDI) risk on GSK2636771 via OATP transporter inhibition by enzalutamide is considered low due to high permeability of GSK2636771.

Section 1.4.2 Benefit Assessment

REVISED TEXT

2nd paragraph, 1st bullet:

- Further treatment with enzalutamide may continue to provide benefit as seen from the limited data suggesting some evidence of response in patients receiving abiraterone following abiraterone, enzalutamide following abiraterone, and from abiraterone following enzalutamide. Rate of growth may still be lower with enzalutamide than without enzalutamide (precedent from trastuzumab beyond progression). **A 14-day run-in period of treatment with enzalutamide monotherapy will be continuous with prior enzalutamide therapy, with the exception of an allowed 30 day drug holiday from enzalutamide treatment, in order to achieve near-steady state enzalutamide exposure.**

Section 1.5.3 Dose Rationale

REVISED TEXT

5th paragraph: A dose of 400 mg **of GSK2636771** once daily was determined to be the MTD and was selected as the recommended Phase II dose (RP2D) for GSK2636771 monotherapy treatment based on safety, PK, and pharmacodynamic (PD) data from Study P3B115717. The proposed starting dose of GSK2636771 in the present study will be 300 mg once daily which is 75% of the RP2D as a single agent determined in Study P3B115717. The starting dose for the present study is lower than the monotherapy RP2D to decrease the probability of overlapping toxicities with GSK2636771 and enzalutamide. Preliminary results from Study P3B115717 indicate that 300 mg once daily of GSK2636771 will result in systemic exposure that resulted in effects consistent with pathway inhibition.

NEW TEXT

6th paragraph: **For enzalutamide, the approved dose of 160 mg once daily was selected. Given the long half-life of enzalutamide, a run-in period of 14 days is included in the study design. The intent of this run-in period is to achieve near-steady state plasma concentrations of enzalutamide prior to initiating combination therapy with GSK2636771.**

Section 2.2 Objectives and Endpoints

REVISED TEXT

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of GSK2636771 + enzalutamide administered orally once daily continuously in subjects with mCRPC.	• AEs, SAEs, DLTs, and changes in laboratory values, ECGs, and vital signs (BP, temperature and ~~pulse~~ **heart** rate)
• To determine the RP2D of orally administered GSK2636771 + enzalutamide in subjects with mCRPC.	• Safety and tolerability **as assessed by AEs, SAEs, DLTs, and changes in laboratory values, ECGs, and vital signs (BP, temperature and heart rate)**

Section 3 Investigational Plan

REVISED TEXT

This is a Phase I, open-label, non-controlled, non-randomized dose-escalation, multicenter study to determine the RP2D of the oral PI3Kβ inhibitor, GSK2636771 in combination with enzalutamide in subjects with mCRPC. The study will be conducted in two phases: the Dose Escalation Phase and the Dose Expansion Phase. **Each phase of the study will consist of a pre-screening period and three treatment periods: Enzalutamide Run-In Period, Combination Treatment Period and Treatment Continuation Period.**

Subjects with PTEN deficient mCRPC (determined during pre-screening), who have documented progression per Prostate Cancer Working Group 2 (PCWG2) criteria (either by Response Evaluation Criteria in Solid Tumors [RECIST] 1.1, prostate-specific antigen [PSA] progression, and/or progression in bone), will be enrolled in the Dose Escalation Phase and Dose Expansion Phase of the study.

~~In the Dose-Escalation Phase, subjects will be enrolled to receive GSK2636771 + enzalutamide and will be approved based on review of available screening data by the GSK Medical Monitor and study manager. Dosing will be conducted in 28 day treatment periods. Decisions for dose determination for subsequent cohorts will be documented and maintained by each site and in the GSK Master Study Files.~~

In the Dose Escalation Phase, subjects will be enrolled into dose-finding cohorts to evaluate the safety and PK to guide the selection of the RP2D of GSK2636771. Dosing decisions will be based on all available data at the end of each DLT reporting period (the first 28 days of combination treatment). Decisions for dose determination for subsequent cohorts will be documented and maintained by each site and in the GSK Trial Master Files (TMF).

In the Dose Expansion Phase, subjects will be assigned to receive GSK2636771 at the MTD or RP2D determined in the Dose Escalation Phase while continuing treatment with enzalutamide to evaluate the long-term safety of the combination as well as the 12-week non-PD rate.

Safety Assessments: Throughout the study, safety will be assessed through standard measures, including physical examinations, vital signs, clinical laboratory tests, 12-lead ECGs and monitoring of AEs. Efficacy will be assessed by physical examination, computed tomography (CT) scan or magnetic resonance imaging (MRI), radionuclide bone scans, circulating tumor cells (CTC) enumeration, and PSA. Pharmacokinetic (PK) blood samples will be collected from all subjects to evaluate if there is an effect of GSK2636771 on the PK of enzalutamide and to quantify the systemic exposure to GSK2636771.

Clinical Response Assessments: The determination of clinical response, including disease progression, will be assessed by both the PCWG2 criteria (see Section 8.8.2). The assessment of the 12 week non-PD-rate in the dose expansion phase will also be determined by PCWG2 criteria (either by RECIST 1.1, PSA progression, and/or progression in bone).

Biomarker Assessments: Planned biomarker assessments include: 1) Identify potential predictive biomarkers (protein, DNA, RNA based) in archival tumor tissue/pre-dose biopsies; 2) enumeration of CTCs in circulation and evaluation of alterations in AR or PTEN genes (or other genomic markers) in isolated CTCs; 3) Assessment of gene mutations in cfDNA and other soluble markers in plasma to better understand clonal evolution and other predictive circulating biomarkers; and 4) understand the mechanism of resistance in tumor tissues biopsies (optional) at time of progression.

~~Subjects will continue study treatment until clinical benefit is no longer apparent, in the opinion of the treating physician, or until unacceptable AE, withdrawal of consent, or death. A post-treatment follow-up visit will be performed within 30 days of the last dose of study treatment(s). The study will be considered completed approximately 6 months after the last subject begins study treatment. However, based on emerging data, the study may continue to collect further efficacy data if warranted.~~

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Tables (Section 8.1) are essential.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study ~~Procedures~~ **Reference** Manual (**SR~~P~~M**). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

Section 3.1 Prescreening and Screening (New Section)

NEW TEXT (originally in Section 3.2):

All subjects will be required to undergo pre-screening to determine the PTEN deficiency status of their tumor at the GSK selected laboratory.

- **Pre-screening may be performed prior to confirmation of progression on enzalutamide**
- **Subjects will be required to sign a separate Pre-Screening Informed Consent Form (ICF) to allow for pre-screening of archived or fresh tumor biopsy samples**
- **Details of the PTEN requirements are provided in SRM.**

Subjects with PTEN-deficient tumors may enter into Screening for the study. Subjects meeting all screening criteria (Section 4.1.2 and Section 4.1.3) may enroll into the Treatment Periods of the study.

Section 3.2 Treatment Periods (New Section)

Section 3.2.1 Enzalutamide Run-In Period (New Section)

NEW TEXT

Subjects will be enrolled in the 14-day run-in period and receive enzalutamide monotherapy at the approved dose of 160 mg once daily. The intent of this run-in period is to achieve near-steady state plasma concentrations of enzalutamide prior to initiating combination therapy with GSK2636771.

Subjects who experience an intolerable toxicity causing a dose interruption or dose reduction during the Enzalutamide Run-In Period will require approval from the GSK Medical Monitor in order to continue in the study. Those subjects not eligible for treatment in the Combination Treatment Period will not be considered in the evaluation of DLTs and may be replaced.

Subjects who discontinue the study during the Enzalutamide Run-In Period will be asked to complete the post-treatment follow-up visit within 30 days of the last dose of enzalutamide.

Section 3.2.2 Combination Treatment Period (New Section)

NEW TEXT

Subjects who complete the Enzalutamide Run-In Period will begin oral GSK2636771 treatment on Week 1, Day 1 of the Combination Treatment Period while continuing to receive enzalutamide to evaluate safety of the combination therapy.

Section 3.2.3 Treatment Continuation Period (New Section)

NEW TEXT

Subjects will continue to receive the combination treatment of GSK2636771 + enzalutamide from Week 5 and thereafter will be seen in the clinic every 4 weeks. Subjects will continue study treatment until clinical benefit is no longer apparent, in the opinion of the treating physician, or until unacceptable AE, withdrawal of consent, permanent discontinuation of treatment, or death.

The study will be considered completed approximately 6 months after the last subject begins study treatment. However, based on emerging data, the study may continue to collect further efficacy data if warranted.

Section 3.3 Post-Treatment Follow-Up

REVISED TEXT, 2nd paragraph

The dosing of enzalutamide will be administered at the US FDA approved dose (refer to the Prescribing Information for enzalutamide [Xtandi, 2013]. Study treatment will continue until there is no longer clinical benefit, in the opinion of the investigator, or until an unacceptable AE (including stopping criteria outlined in Section 7.2), withdrawal of consent, **permanent discontinuation of treatment,** or death occurs. Investigators will use the PCWG2 criteria to determine clinical response to each treatment.

NEW TEXT

A post-treatment follow-up visit will be performed within 30 days of the last dose of study treatment(s) for all subject who permanently discontinue study treatments, during the Enzalutamide Run-In Period (and/or do not enter the Combination Treatment Period), or for those who permanently discontinue study treatments during the Combination Treatment or Treatment Continuation Period due to disease progression.

Subjects who withdraw from the study during the Combination Treatment or Treatment Continuation Period *without* disease progression should complete the Extended Follow-up Visits where they will be contacted every 3 months (±14 days) until disease progression, death, withdrawal of consent, or subject is lost to follow-up. Contact may include a clinic visit, a telephone contact, or an e-mail. The initiation of any new anti-cancer treatments and date of last contact should be documented. Subjects who discontinue the Extended Follow-Up Visits prior to disease progression, death, or withdrawal of consent should have a Post-Extended Follow-Up/EOS Visit performed.

Section 3.4 Dose Escalation Phase

REVISED TEXT

1st paragraph: In the Dose-Escalation Phase, the dose of GSK2636771 will follow a modified 3+3 dose-escalation procedure to evaluate the safety and PK for each

combination dose level and to guide selection of the RP2D of the combination. ~~Subjects with PTEN deficient mCRPC who are receiving a stable dose of enzalutamide with recent demonstrated progression per PCWG2 criteria (either by RECIST 1.1, PSA progression, and/or progression in bone) will be enrolled.~~

2nd paragraph, last sentence: Dose escalation will proceed with the increment of dose increase **or decrease as** determined by toxicity rules outlined in Table 1.

Section 3.4.2 Alternative Dosing Schedule

REVISED TEXT

Alternative schedules may be evaluated if emerging data suggest that continuous daily dosing will result in excessive toxicity. Only those alternative schedules exploring dosing less frequent than current dosing schedule will be evaluated. **If alternative dosing schedules are explored, PK sampling times will be modified to reflect the new dosing schedule.**

Section 3.4.3 Definition of Dose Limiting Toxicity

NEW TEXT

1st paragraph: The DLT criteria apply only during the dose finding stage, and impacts the decisions around whether the MTD has been determined, and/or decisions around whether to escalate or de-escalate the next dose level, but do not apply to the mandated management of an individual subject as with the liver stopping criteria.

Last paragraph: Subjects who experience an intolerable toxicity causing a dose interruption or dose reduction during the Enzalutamide Run-In Phase (before the start of GSK2636771 combination treatment) will require approval from the GSK Medical Monitor in order to continue in the study. Those subjects not eligible for the combination phase will not be considered in the evaluation of DLTs and may be replaced.

REVISED TEXT

Subjects who fail to receive at least 75% of protocol-specified study treatment during the DLT reporting period (the first 28 days **of combination** treatment), for reasons OTHER than toxicity, will be replaced if data from the replacement subject could impact the dose selection criteria.

An event will be considered a DLT if the event is attributed (definitely, probably or possibly) to study treatment, **occurs within** the first 28 days of **combination** treatment **(DLT reporting period),** and meets one of the following criteria:

Bullets 5 and 6:

- Alanine aminotransferase (ALT) >3 times upper limit of normal (ULN) with bilirubin >2 times ULN ~~(or ALT >5 times ULN and 150% of baseline ALT, if enrolled with liver metastases/tumor infiltration at baseline)~~ **(or ALT ≥3 times ULN and ≥1.5 times baseline ALT value, if enrolled with liver metastases/tumor infiltration at baseline), together with bilirubin ≥2 times ULN)**

Any Grade 2 or greater toxicity per CTCAE v4.0 that **occurs beyond the 28-day DLT reporting period which** in the judgment of the investigator and GSK Medical Monitor would be considered dose-limiting.

Section 3.4.4 Maximum Tolerated Dose

REVISED TEXT

The MTD is defined as the highest dose at which **no more than one of** ~~one or fewer of up to~~ 6 subjects experience a DLT during the first 28 days of combination therapy. The MTD will be exceeded if 2 or more subjects in a cohort of up to 6 subjects experience a DLT.

Section 3.5 Dose Expansion Phase

REVISED TEXT

First sentence: Enrollment in the Dose Expansion Phase of the study may begin once the MTD **and RP2D** have been determined ~~at the RP2D~~ in the Dose Escalation Phase.

Section 3.6.1 Evaluation of Futility

REVISED TEXT

Futility will be evaluated in the Dose Expansion Phase of the study. The methodology is based on the predictive probability of success if enrollment continues to 20 subjects [Lee, 2008]. The predictive probability design is similar to a Green-Dahlberg design in that it allows for early stopping for futility. The differences are that the predictive probability design allows for evaluation of stopping rules after each subject, rather than at only two stages, once a minimum number of subjects are evaluable. In this particular study, we will stop only for futility. While the two designs have similar type I and type II error rates, the probability of early termination is greater with the predictive probability design.

After 10 subjects have been enrolled to examine safety and 12-week non-PD rate, the number of subjects who have not progressed in 12 weeks will guide further enrollment according to the rules summarized in Table 3. ~~A maximum of 20 subjects will be enrolled at the RP2D.~~ All available data will be considered in making enrollment decisions.

Section 3.7 Continued Treatment

REVISED TEXT

A subject may continue study treatment until the treatment discontinuation criteria are met (see Section 5.2). **Additional guidelines regarding dose modifications are provided in Section 7.1.** ~~Prior to administration of additional study treatment beyond the first 28 days (the DLT reporting period), clinically significant AEs should be resolved to baseline or Grade 1.~~

Section 3.8 Treatment Assignment

DELETED TEXT

~~Each site will be given a subject number range (range will be provided in the SRM). Upon completion of all required pre-screening and screening procedures and assessments, eligible subjects will be enrolled by the study team. Subjects will be identified by a unique subject number that will remain consistent for the duration of the study.~~

NEW TEXT

Each subject will be assigned a unique subject number that will remain consistent for the duration of the study. This number will be assigned sequentially from a range of subject numbers provided for each site in the SRM. Upon completion of all required pre-screening and screening procedures and assessments, eligible subjects must be approved for enrollment by a member of the study team according to the procedures detailed in the SRM.

Section 4.1.1 Number of Subjects

REVISED TEXT

A total of approximately 44 subjects will be enrolled in this study. ~~In the Dose Escalation Phase, additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels. The sample size planned for the Dose Expansion Phase is not driven by statistical considerations as the cohort is meant to further understand the safety implications of enrolling subjects to combination therapy for an extended period of time. See Section 13.2 for sample size assumptions.~~

Dose Escalation Phase: The number of dose levels and the level at which the MTD is reached cannot be determined in advance. An adequate number of subjects will be enrolled to establish the recommended dose for further study. It is estimated that approximately 24 subjects will be needed for the Dose Escalation Phase.

Dose Expansion Phase: In the Dose Expansion Phase, it is estimated that approximately 20 subjects will be enrolled, **with evaluation for futility after the first 10 subjects have completed 12 weeks of treatment (see Section 3.5.1).** ~~although if the first 10 subjects progress with mCPRC, the dose expansion will be stopped.~~

The sample size planned for the Dose Expansion Phase is not driven by statistical considerations as the cohort is meant to further understand the safety implications of enrolling subjects to combination therapy for an extended period of time. See Section 13.2 for sample size assumptions.

Section 4.1.2 Inclusion Criteria #1, #2, #3, #5, #7, #8, #9, #11 and #12

NEW TEXT

New Inclusion Criteria #8 (all subsequent criteria have been renumbered): **Has not been without enzalutamide treatment for >30 days prior to enrollment**

REVISED TEXT

1. Signed written informed consent

   NOTE: Separate ICFs must be signed prior to the pre-screening and screening procedures.

2. Males ≥18 years of age (at the time **written** consent is obtained **for pre-screening**)

3. Histologically or cytologically confirmed diagnosis of prostate adenocarcinoma, surgically castrated or continuous medical castration (**for ≥8 weeks prior to Screening**)

5. PTEN-deficient tumor as documented from archived or fresh (from **pre-treatment** biopsy) tumor tissue analyzed by a GSK selected laboratory

7. Has completed at least 12 weeks of prior continuous therapy with enzalutamide

~~**NOTE:** A 30 day or less treatment (enzalutamide) holiday will be permitted prior to Screening.~~

~~8. Most recent enzalutamide dose received is 160 mg once daily with no change in dose for at least 2 weeks prior to enrollment~~

9. Has **documented disease progression** ~~progressive disease~~ ~~at time of enrollment~~ **following treatment with enzalutamide at a time of Screening.**

NOTE: Disease progression is defined as one or more of the following criteria:

11. Adequate baseline organ function **at the time of Screening** defined as:

Renal	
Urine Protein (via dipstick)[2]	**0/+1**
UPC[3,4]	**<0.2**
Serum Creatinine	≤ULN
OR	
Estimated Serum Creatinine Clearance[5]	≥60 mL/min
OR	
24-hr Urine Creatinine Clearance	≥60 mL/min
Cardiac	
LVEF	≥50% by ECHO or MUGA
Other	
Serum Phosphate[6]	**≤Grade 1**
Serum Calcium (corrected)	**WNL**

Abbreviations: ANC, absolute neutrophils count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; **CTCAE, Common Terminology Criteria for Adverse Events**; ECHO, echocardiogram; INR, international normalization ratio; **LLN, lower limit of normal**; LVEF, left ventricular ejection fraction; MUGA, multigated acquisition scan; PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; UPC, urine protein to creatinine ratio; **WNL, within normal limits**

1. If ALT or bilirubin values are outside range listed due to Gilbert's syndrome or asymptomatic gallstones, subject remains eligible.
2. **If subject's urine protein is >1+ (via dipstick), then UPC ratio will be calculated. Subject will be considered eligible for study if UPC ratio is <0.2.**
3. **UPC ratio is only to be calculated if subject's urine protein is >1+ via dipstick.**
4. **The UPC value will not be used to determine eligibility for subjects who are unable to obtain uncontaminated urine samples due to their disease.**
5. Estimated by the Cockcroft and Gault Formula (see Appendix 3).
6. **Per CTCAE v4.0, Grade 1 hypophosphatemia is <LLN – 2.5 mg/dL (<LLN – 0.8 mmol/L)**

NOTE: Laboratory results obtained during Screening should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the investigator may opt to retest the subject and the subsequent within range screening result may be used to confirm eligibility.

12. Male subject with a female partner of childbearing potential **or pregnant** must ~~have either a prior vasectomy or~~ agree to use **two acceptable methods** ~~effective~~ of contraception as described in Section 11.1 from time of Screening until 3 months after the last dose of study treatment.

DELETED TEXT

~~12. Must have a QT interval corrected for heart rate according to Fridericia's formula (QTcF) <470 msec or <480 msec with bundle branch block (BBB).~~

~~**NOTE:** For subject eligibility, withdrawal, and for purposes of data analysis, QTcF will be used. The QTcF should be based on single or averaged QTc values of triplicate ECGs obtained over a brief recording period.~~

Section 4.1.3 Exclusion Criteria #1, #4, #5, #6, #11, #15, #16, #18 and #22

REVISED TEXT

1. Prior treatment with:

Exception: Subjects may remain on luteinizing hormone releasing hormone (LHRH) agonists (i.e., leuprolide, goserelin, triptorelin or histrelin) **and AR antagonists (e.g., bicalutamide, flutamide, nilutamide).**

Exception: Subjects must have **received** prior treatment with enzalutamide.

- Any PI3K, AKT or mammalian target of rapamycin (mTOR) inhibitors
- Investigational drug(s) **(other than enzalutamide)** within 30 days or 5 half-lives, whichever is longer, prior to enrollment

4. Any unresolved ≥Grade 2 **toxicity** (per CTCAE v4.0) ~~toxicity~~ from previous anti-cancer therapy at the time of enrollment, except alopecia or Grade 2 anemia (if hemoglobin is >9.0 g/dL)

5. ~~Hypophosphatemia Any ≥Grade 2 hypophosphatemia (per CTCAE v4.0) at the time of enrollment~~

~~6. Serum calcium ≥Grade 1 (per CTCAE v4.0) at time of enrollmenton Day -1, unless ionized calcium is within normal range~~

11. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at **time of** Screening or within 3 months prior to **enrollment** ~~first dose of study treatment~~

15. History of seizure or any condition that may predispose subject to seizure (e.g., prior cortical stroke or significant brain trauma). History of loss of consciousness or transient ischemic attack within 12 months of ~~randomization~~**enrollment**

18. Poorly controlled hypertension (defined as systolic blood pressure [SBP] of ≥150 mmHg or diastolic blood pressure [DBP] of >100 mmHg based on a mean of three measurements at approximately 2-minute intervals)

> **NOTE:** Initiation or adjustment of antihypertensive medication(s) is permitted **if done** ~~within~~ 30 **or more** days prior to enrollment.

22. Exposure to more than 4 **investigational medicinal products** (IMPs) within 12 months prior to ~~the first dose of study treatment~~ **enrollment**

NEW TEXT

16. **Has a QTc >450 msec or QTc >480 msec for subjects with bundle branch block (BBB)**

    NOTES: The QTc is the QT interval corrected for heart rate by Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read.

    The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial.

    For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).

Section 5.2 Permanent Discontinuation of Study Treatment(s)

REVISED TEXT

~~Subjects may receive study treatment until disease progression, unacceptable toxicity, including meeting stopping criteria for liver chemistry as defined in Section 7.2.2, or death.~~ Study treatment(s) will be permanently discontinued for any of the following reasons:

- Disease progression

  NOTE: Subjects must meet the PCWG2 guidelines for disease progression to avoid premature discontinuation of study treatment(s).

  - ***Treatment Discontinuation due to PSA rise:*** **Following PCWG2 guidelines, subjects should not be discontinued from study treatment(s) solely due to PSA rise during the first 12 weeks of treatment (Section 8.8.2.1).**

  - ***Treatment Discontinuation due to Bone Scan changes:*** **Subjects should not be discontinued from study treatment(s) due to the occurrence of bone scan changes in the first 12 weeks that do not meet PCWG2 guidelines for progression (Section 8.8.2.2).**

- Unacceptable toxicity (including meeting liver chemistry stopping criteria as defined in Section 7.2.2)

  NOTE: If the subject voluntarily discontinues from treatment due to toxicity, 'adverse event' will be recorded as the primary reason for permanently discontinuation on the eCRF.

- Substantial protocol deviation(s)
- Death
- Investigator's discretion
- Lost to follow-up
- Intercurrent illness that prevents further administration of study treatment(s)
- Withdrawal of consent by subject or proxy for further treatment and/or data collection
  - If subject withdraws consent for further treatment, the subject should return for Post-Treatment Follow-up Visit as indicated in the Time and Events Tables (Section 8.1).
  - If subject withdraws consent for further treatment and data collection, then no additional study visits, including a post-treatment follow-up visit, or data collection should occur. All samples collected for the biomarker analysis at the time of withdrawal will proceed for analysis to meet the intended objectives defined in this protocol**, unless consent for further analyses is withdrawn by the subject**.
- Study closure or termination

If study treatment(s) is/are permanently discontinued, the subject will not be allowed to be retreated. The primary reason for permanently discontinuing study treatment(s) must be documented in the subject's medical records and electronic case report form (eCRF).

All subjects **who have study treatment(s) permanently discontinued** will have safety assessments at the time of discontinuation and during post-study treatment follow-up as specified in Time and Events Tables (Section 8.1).

Treatment Discontinuation without Disease Progression: All subjects who permanently discontinue study treatment(s) without disease progression should be followed for progression **in the Extended Follow-Up Visits** ~~according to the protocol schedule~~ until:

- A new anti-cancer therapy is initiated, or
- Disease progression occurs, or
- **Subject withdrawal, or**
- Death

~~Treatment Discontinuation due to PSA rise:~~ ~~Following PCWG2 guidelines, subjects should not be discontinued from study treatment(s) solely due to PSA rise during the first 12 weeks of treatment (Section 8.8.2.1).~~

~~Treatment Discontinuation due to Bone Scan changes:~~ ~~Subjects should not be discontinued from study treatment(s) due to the occurrence of bone scan changes in the first 12 weeks that do not meet PCWG2 guidelines for progression (Section 8.8.2.2).~~

Section 5.3 Study Completion

REVISED TEXT

A subject will be considered to have completed the study if the subject dies or otherwise progresses during the study treatment or post-treatment follow-up period.

A subject will be considered to have withdrawn from the study ~~if the subject has not died or progressed and is lost to follow-up, has withdrawn consent, or at the investigator's discretion is no longer being followed.~~

Section 6.1 GSK2636771 GSK Investigational Product

REVISED TEXT

Dosing Instructions:	~~Dose with approximately 200 mL of water. GSK2636771 should be taken prior to enzalutamide in the morning (once last PK sample is obtained morning dosing is not required). Subjects should fast for at least 1hr before and 2 hrs after dosing.~~ See Section 6.3 for dosing instructions ~~on days when PK blood draws will occur~~.

Section 6.2 Enzalutamide Non-GSK Product

DELETED TEXT

~~Enzalutamide (Xtandi) will be sourced locally from commercial stock for sites in countries where it is approved (e.g., US). The contents of the label will be in accordance with all applicable regulatory requirements.~~

~~Investigators are responsible for ensuring that subjects receive supplies of enzalutamide for the entire duration of the study, except in countries where Regulatory Authorities mandate that the Sponsor must supply all study treatment(s) required for study participation.~~

NEW TEXT

Initially, in countries where it is approved (i.e., US), sites will need to obtain enzalutamide (Xtandi) from local commercial stock in order to provide enrolled subjects with an adequate supply of enzalutamide while on study.

In countries where regulatory authorities mandate that the Sponsor must supply all study treatment(s) required for study participation, GSK will provide an adequate supply of enzalutamide (from commercial stock) directly to the site for enrolled subjects.

Enzalutamide will be provided to subjects at no cost to begin taking enzalutamide on the first day (Day 1) of the Enzalutamide Run-In Period and throughout their participation in the study. If a subject does not qualify for entry into the study based on the tests or assessments performed during the pre-screening and screening periods, then no further supply of enzalutamide will be provided to them.

The sourcing of enzalutamide from commercial stock will continue until which time (estimate within first quarter of 2015) GSK will begin supplying all sites with an adequate inventory of commercial, US sourced enzalutamide; an appropriate amendment will be made to the Quality section of the IND and CTA.

The contents of the label will be in accordance with all applicable regulatory requirements.

Route/Administration/ Duration:	Oral/once daily, **within 5 minutes of GSK2636771 administration/** continuous until treatment withdrawal

Section 6.3 Administration of Study Treatments

REVISED TEXT

Dosing Time: Subjects will be instructed to take their doses of study treatment **(GSK2636771 and enzalutamide)** at the same time each day if possible (24 hr intervals). Morning dosing is required until the last **serial** PK blood **and plasma** sample are obtained **on Day 29 of Week 5 (Treatment Continuation Period**. **Once the last serial PK sample is obtained, dosing of study treatments can occur anytime during the day. For s**ubjects who wish to switch to evening dosing ~~may do so once the last PK blood sample is obtained. To switch to evening dosing~~, the subject is to delay their next **doses of study treatments** by 12 hrs.

Dosing at Home~~on Non-PK Sampling Days~~: **On days when subjects do not have a scheduled study visit in the clinic, s**ubjects will be instructed to ~~take~~**self-administer**

their doses of study treatments **at home** under fasted conditions, at least 1 hr before or 2 hrs after a meal~~, on days when no PK blood samples are to be drawn~~.

Dosing during the Enzalutamide Run-In Period (Days 1 to 14): **Enzalutamide is the only study treatment taken during the Enzalutamide Run-In Period. The intent of this Enzalutamide Run-In Period is to achieve near-steady state plasma concentrations of enzalutamide prior to initiating combination therapy with GSK2636771. Subjects should be instructed to take their once daily dose of enzalutamide every morning at the same time each day if possible (24-hr intervals) during the Enzalutamide Run-In Period. Specific instructions for the administration of enzalutamide on Day 14 of the Enzalutamide Run-In Period are provided in the *Dosing on PK Sampling Days during the Dose Escalation Phase* section below.**

Dosing on Scheduled Study Visit Days: **Most of the scheduled study visit days during the first 5 weeks of combination treatment will require a pre-dose blood, plasma, and/or urine sample for analysis of PK, CTC, and/or urine electrolytes. On Day 1 of Weeks 8 and 12 during the Treatment Continuation Period, pre-dose blood and plasma samples for analysis of PK are required. On Day 1 of Week 8 and every 8 weeks thereafter during the Treatment Continuation Period, pre-dose blood and urine samples for analysis of CTC (through Week 32 only) and urine electrolytes are also required. Subjects should be instructed to withhold their doses of study treatments on mornings of these scheduled study visits as follows:**

~~***Dosing on PK Sampling Days:*** For dense serial PK days, subjects should fast overnight (at least 8 hrs) and remain fasting the morning of dosing until study treatment is administered. After dosing of study treatment, subjects will continue to fast for an additional 2 hrs. On days when sparse PK samples are collected, subjects should fast for at least 1 hr before and 2 hrs after administration of study treatment.~~

Dosing on PK Sampling Days during the Dose Escalation Phase:

- **Day 14 (Enzalutamide Run-In Period):** the day prior to administration of the first dose of GSK2636771: Subjects will fast overnight (at least 8 hrs) and remain fasting the morning of this study visit. Subjects will be instructed to withhold their dose of enzalutamide on **the morning** ~~prior to the~~ of this study visit. ~~on Day -1.~~ After the pre-dose **PK plasma sample is drawn**~~blood draw is completed~~, subjects will be administered their doses of enzalutamide in the clinic and **will** ~~asked to~~ continue fasting for an additional 2 hrs.

- **Day 29, Week 5 (Treatment Continuation Period):** Subjects will fast overnight (at least 8 hrs) and remain fasting the morning of this study visit. Subjects will be instructed to withhold the doses of study treatment **on the morning of this** ~~prior to the~~ study visit.~~on Day 29 of Wk 5.~~ After the pre-dose pK blood **and plasma samples are drawn** ~~draw is completed~~, subjects will be administered their doses of study treatments in the clinic and ~~asked to~~ **will** continue fasting for an additional 2 hrs.

- **Weeks 8 and 12 (Treatment Continuation Period):** Subjects will be instructed to withhold their doses of study treatment prior to these study visits. **After the pre-dose PK blood and plasma samples are drawn, s**ubjects will ~~have~~ **be administered** their doses of study treatments ~~administered~~ in the clinic ~~after the pre-dose blood draw is completed and~~ under fasted conditions, at least 1 hr before or 2 hrs after a meal **(an overnight fast is not required).**

Dosing on PK Sampling Days during the Dose Expansion Phase:

- **Day 29, Week 5 (Treatment Continuation Period):**
    - Subjects scheduled for a *morning* clinic visit will be instructed to withhold the doses of study treatments prior to this study visit ~~on Day 29 of Wk 5~~. **After the pre-dose PK blood and plasma samples are drawn, subjects** ~~Study treatments~~ will be administered **their doses of study treatments** in the clinic ~~after the pre-dose blood draw is completed and~~ under fasted conditions, at least 1 hr before or 2 hrs after a meal **(an overnight fast is not required).**
    - Subjects scheduled for an *afternoon* clinic visit will be instructed to take their doses of study treatments at the usual time **on the morning of this study visit** ~~and under fasted conditions~~, at least 1 hr before or 2 hrs after a meal **(an overnight fast is not required)**.
- **Weeks 8 and 12 (Treatment Continuation Period):** Subjects will be instructed to withhold the doses of study treatment prior to the study visit during Wks 8 and 12. Subjects will have their doses of study treatments administered in the clinic after the pre-dose blood draw is completed and under fasted conditions, at least 1 hr before or 2 hrs after a meal.

Dosing on CTC and Urine Electrolyte Sampling Days: **Subjects will be instructed to withhold their doses of study treatments on the morning of study visits when a blood or urine sample is to be obtained for analysis of CTCs and/or urine electrolytes, respectively. After the pre-dose blood sample is drawn and/or the pre-dose urine sample is collected, subjects will have their doses of study treatments administered in the clinic, at least 1 hr before or 2 hrs after a meal (an overnight fast is not required).**

Vomiting: If a subject vomits after taking study treatment(s), the subject should be instructed NOT to retake the dose and should take the next scheduled dose of study treatment(s). If vomiting persists, the subject should contact the investigator.

Missed Doses: If subject misses a dose of study treatment(s), the subject should be instructed to take the missed dose as soon as they realize it was missed, but not take the missed dose if there are less than 12 hrs until the next dose. The missed dose should be recorded in the **subject diary for either GSK2636771 or enzalutamide and in the** eCRF.

Section 6.3.1 GSK2636771

REVISED TEXT

For this study, the starting dose of GSK2636771 is 300 mg taken orally once daily.

GSK2636771 ~~should~~ **is to** be administered **within 5 minutes** prior to enzalutamide and under fasted conditions, either 1 hr before or 2 hrs after a meal **and** with approximately 200 mL of water **(unless otherwise instructed in Section 6.3 for study visit days when PK, CTC, or urine electrolyte sampling is required).**

Subjects shall abstain from ingestion of any food or drink containing grapefruit and grapefruit juice, Seville oranges or pomelos within 7 days prior to the first dose of GSK2636771 **(Week 1, Day 1 of Combination Treatment Period)** until the last dose of study treatment.

Section 6.3.2 Enzalutamide

REVISED TEXT

Per the product prescribing information for enzalutamide [Xtandi, 2013], the recommended dose of enzalutamide 160 mg (four 40 mg capsules) taken orally once daily will be administered during this study. ~~Enzalutamide may be taken with or without food except on days of PK sampling when enzalutamide should be administered under fasted conditions, either 1 hr before or 2 hrs after a meal.~~

Enzalutamide may be taken with or without food on each day of the Enzalutamide Run-In Period (Days 1-13). Specific instructions for the administration of enzalutamide on Day 14 of the Enzalutamide Run-In Period may be found in Section 6.3. Once combination therapy (GSK2636771 + enzalutamide) begins on Week 1, Day 1 of the Combination Treatment Period, enzalutamide ~~should~~ **is to** be administered within 5 minutes **after** ~~of~~ the administration of GSK2636771~~. When administered with GSK2636771, enzalutamide should be administered~~ **and** under fasted conditions, either 1 hr before or 2 hrs after a meal (unless otherwise instructed ~~due to PK sampling; see Section 6.3).~~ **in Section 6.3 for study visit days when PK, CTC, or urine electrolyte sampling is required).**

Section 6.4 Handling and Storage of Study Treatments

REVISED TEXT

Handling: Under normal conditions of handling and administration, the study treatments are not expected to pose significant safety risks to site staff. Material Safety Data Sheets (MSDSs) for GSK2636771 **and enzalutamide** describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

Storage: All study treatments (GSK2636771 and enzalutamide) must be stored in a secure area under the ~~appropriate physical~~**following** conditions for each product: ~~Access~~

~~to and administration of study treatments will be limited to the investigator and authorized site staff. Study treatments must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.~~

- GSK2636771: Store under appropriate physical conditions for the product **as stated on the label**. **Refer to the SRM regarding temperature excursions.**

- Enzalutamide: ~~Recommended storage is 20°C to 25°C (68°F to 77°F) in a dry place. Excursions permitted from 15°C to 30°C (59°F to 86°F).~~ **Store under appropriate physical conditions for the product as stated on the label**. **Refer to the SRM regarding temperature excursions.**

Access to and administration of study treatments will be limited to the investigator and authorized site staff. Study treatments must be dispensed or administered only to subjects who qualify for entry in this study and in accordance with the protocol. Subjects should be reminded that all study treatments should be stored at home out of the reach of children.

~~All study treatments should be stored out of the reach of children.~~

Section 6.7 Treatment of Study Treatment Overdose, 4th paragraph

REVISED TEXT

A plasma **or blood** sample for PK analysis of one or more study treatments may be requested by the GSK Medical Monitor on a case-by-case basis. This plasma **or blood** sample should be collected as soon as possible, but within 7 days from the date of the last dose of study treatment (or suspected overdose).

Section 7 Dose Modifications, Stopping Criteria, and Management Guidelines for Specific Events Associated with GSK2636771

REVISED TEXT

The following dose modifications, stopping criteria, and management guidelines for specific events **associated with GSK2636771** are provided as guidance and should not act as a replacement for sound clinical judgment. The investigator should use clinical judgment to determine which study treatment may be contributing to the toxicity necessitating dose adjustment, and make the appropriate change for that agent. The severity of AEs will be graded utilizing the CTCAE v4.0. ~~Guidelines for dose modifications and interruptions for management of specific toxicities are provided in this section.~~

If a given toxicity is considered to be related to one specific study treatment by the investigator but not both, then dose modification should only occur with the study treatment associated with the specific toxicity or event of clinical concern.

Section 7.1.1 GSK2636771 (NEW Section Header)

Text moved from Section 7.1 to Section 7.1.1

REVISED TEXT

Dose modification guidelines **for GSK2636771** are outlined in Table 4 for clinically significant toxicities that are deemed related to study treatment but are not addressed specifically in Section ~~7.2~~ **7.3**. ~~If a given toxicity is considered to be related to one specific study treatment by the investigator but not both, then dose modification should only occur with the study treatment associated with the specific toxicity or event of clinical concern.~~

Section 7.2.1 QTc Stopping Criteria

DELETED TEXT

~~If QTcF >500 msec (Grade 3 or 4 QTc prolongation) or uncorrected QT >600 msec (averaged manual overread of 3 ECGs over at least 15 minutes), then the following guidelines should be followed:~~

- ~~Hold study treatments~~
- ~~Discuss with GSK Medical Monitor~~
- ~~Correct any electrolyte abnormalities~~
- ~~If QTcF resolves to ≤ 470 msec, study treatment may be restarted with dose reduction to the next dose level if the investigator and GSK Medical Monitor agree that the subject will benefit from further treatment.~~
- ~~If QTcF does NOT resolve to ≤ 470 msec, discontinue study treatments permanently.~~

NEW TEXT

- **QTc >500 msec**

OR

- **Change from baseline of QTc >60 msec**

For subjects with underlying bundle branch block (BBB), follow the discontinuation criteria listed below:

Baseline QTc with BBB	Discontinuation QTc with BBB
<450 msec	>500 msec
450 – 480 msec	≥530 msec

Section 7.2.2 Liver Chemistry Stopping Criteria

DELETED TEXT

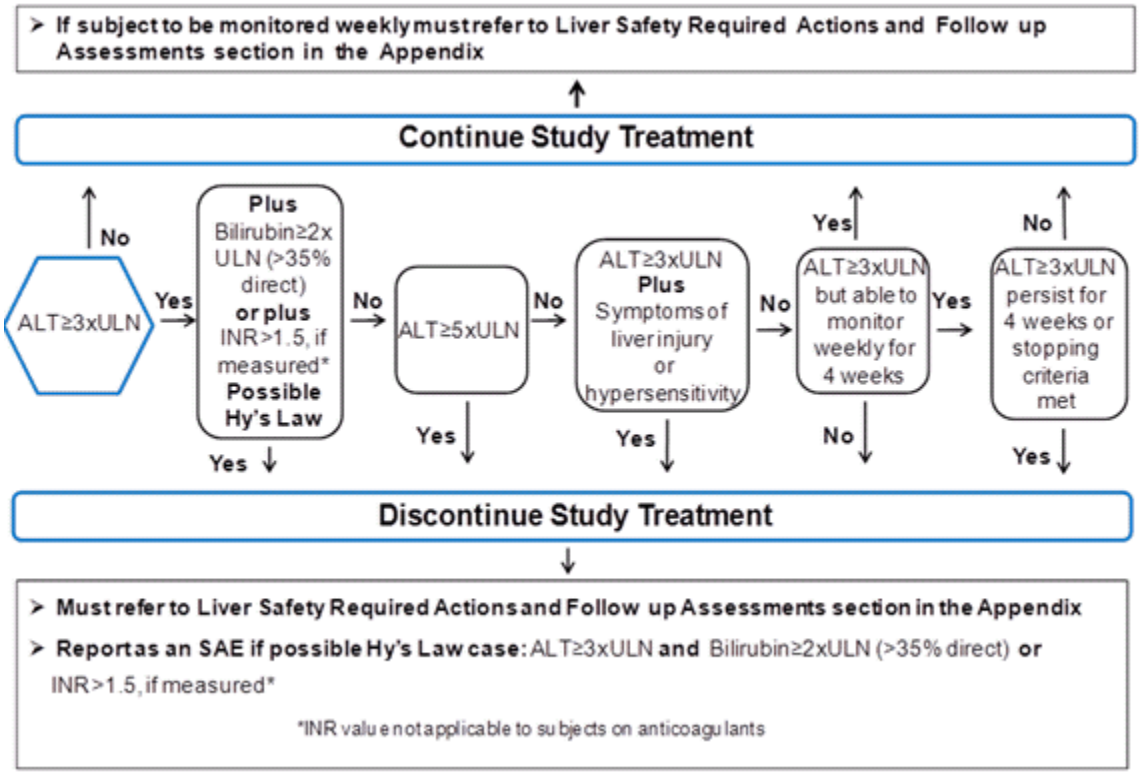
~~Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology during administration of study treatments and the follow-up period. The liver chemistry stopping criteria for subjects with ALT ≤2.5 times ULN at study entry is provided in Section 7.2.2.1 and for subjects with documented liver metastases or tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN in Section 7.2.2.2.~~

NEW TEXT

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the US FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Section 7.2.2.1 Liver Chemistry Stopping and Increased Monitoring Algorithm for Subjects WITH entry criteria ALT ≤2.5 x ULN

DELETED TEXT



~~Liver Safety Required Actions and Follow-up Assessments can be found in Appendix 6.~~

NEW TEXT

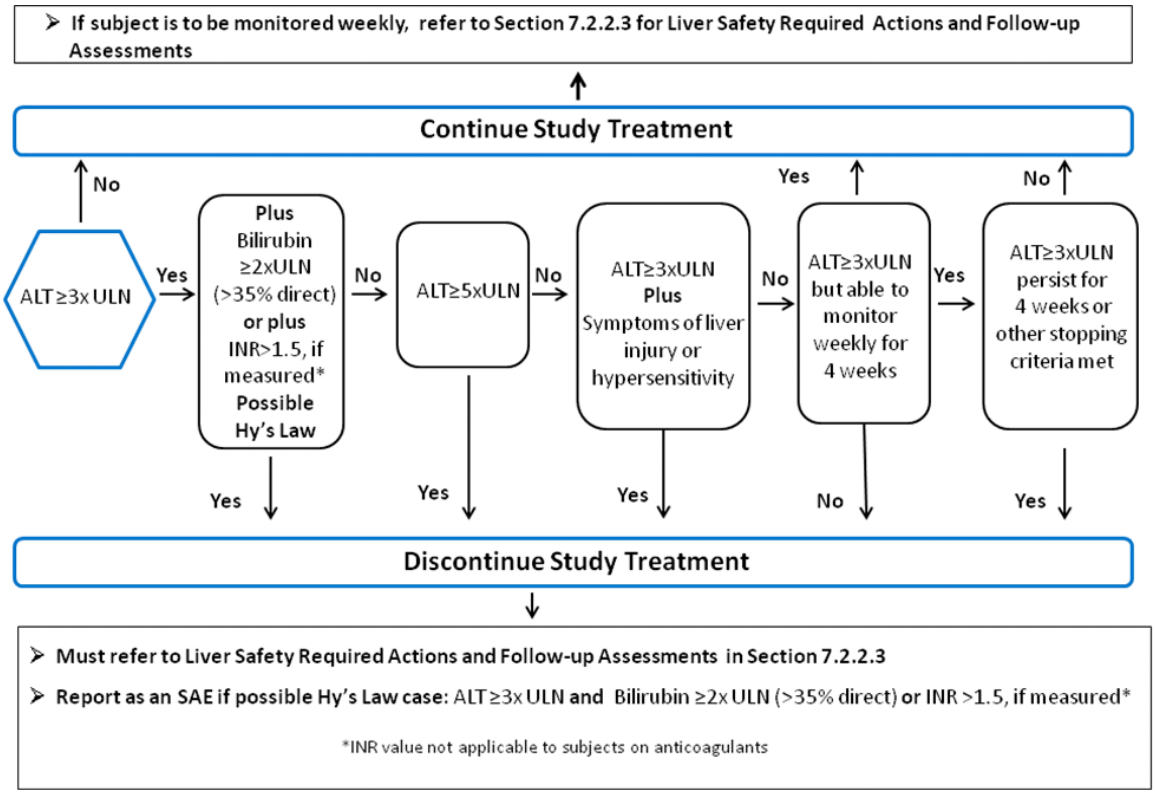


Table 6 Liver Chemistry Stopping Criteria – Liver Stopping Event for Subjects WITH Entry Criteria ALT ≤2.5xULN

ALT absolute	ALT ≥5xULN
ALT Increase	ALT ≥3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin)
INR[2]	ALT ≥3xULN and INR>1.5, if INR measured
Cannot Monitor	ALT ≥3xULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Abbreviations: ALT, alanine aminotransferase; INR, international normalization ratio; SAE, serious adverse event; ULN, upper limit of normal

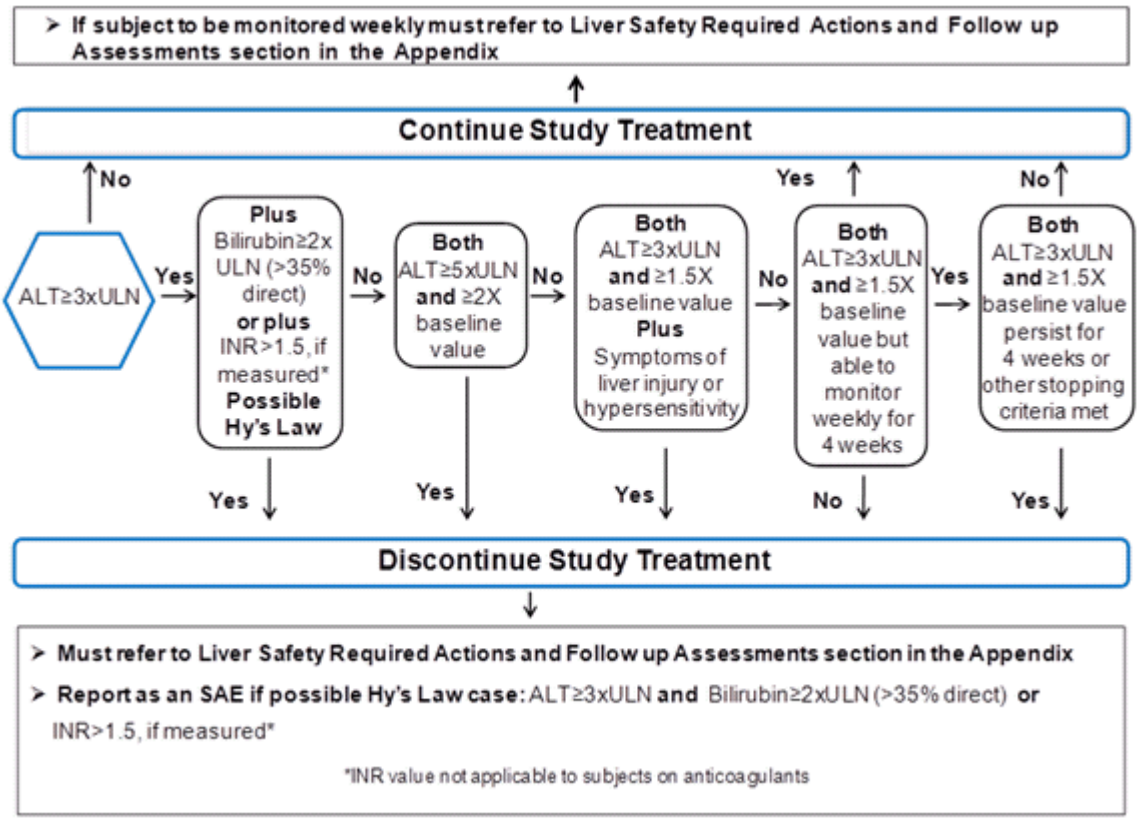
1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥3xULN and bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE

(excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants.

3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).

Section 7.2.2.2 Liver Chemistry Stopping and Increased Monitoring Algorithm including Subjects WITH Documented Liver Metastases/Tumor Infiltration at Baseline AND Entry Criteria ALT>2.5xULN but ≤5xULN

DELETED TEXT



~~Liver Safety Required Actions and Follow-up Assessments can be found in Appendix 7.~~

NEW TEXT

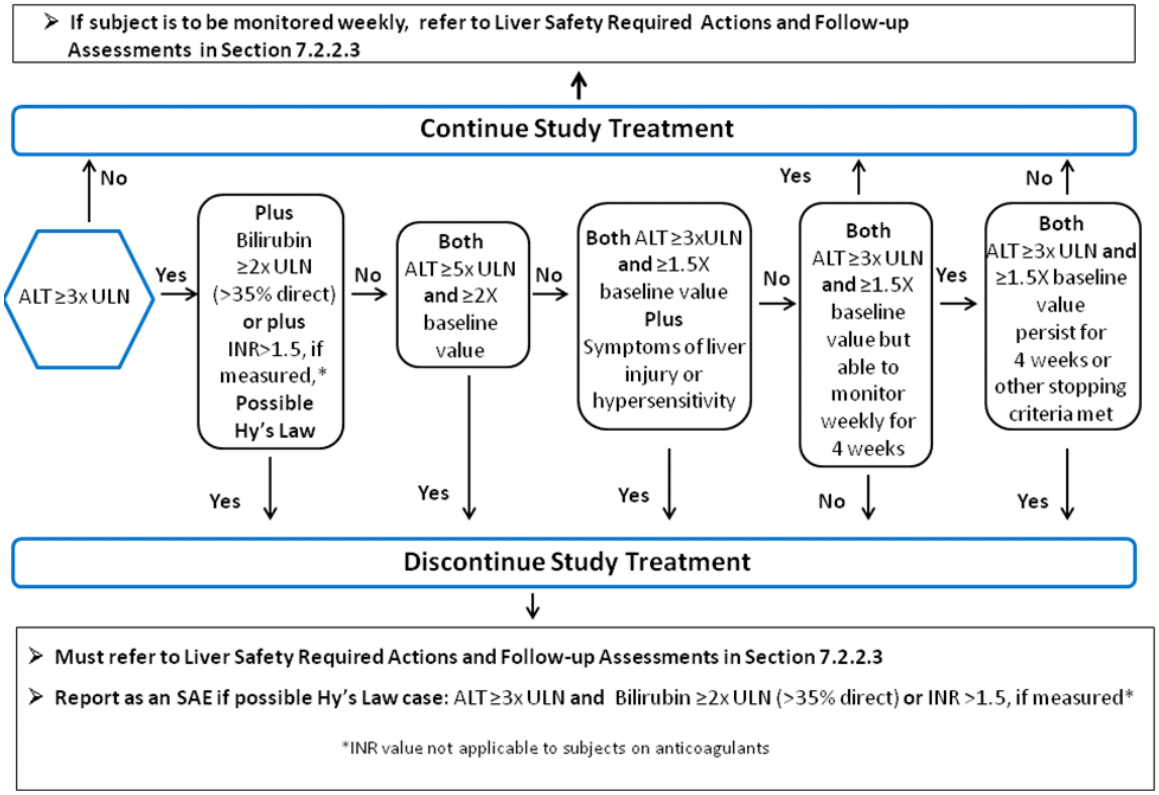


Table 7 Liver Chemistry Stopping Criteria – Liver Stopping Event for Subjects with Documented Liver Metastases/Tumor Infiltration at Baseline AND Entry Criteria ALT>2.5xULN but ≤5xULN

ALT absolute	Both ALT ≥5xULN and ≥2x baseline value
ALT Increase	Both ALT ≥3xULN and ≥1.5x baseline value that persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin)
INR[2]	ALT ≥3xULN and INR>1.5, if INR measured
Cannot Monitor	Both ALT ≥3xULN and ≥1.5x baseline value that cannot be monitored for 4 weeks
Symptomatic[3]	Both ALT ≥3xULN and ≥1.5x baseline value associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Abbreviations: ALT, alanine aminotransferase; INR, international normalization ratio; SAE, serious adverse event; ULN, upper limit of normal

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥3xULN and bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.

2. All events of ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).

Section 7.2.2.3 Liver Safety Required Actions and Follow-up (NEW SECTION)

NEW TEXT

Table 8 Required Actions and Follow-Up Assessments Following ANY Liver Stopping Event

Actions	Follow-Up Assessments
• Immediately discontinue study treatment • Report the event to GSK within 24 hrs • Complete the liver event eCRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow-up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below) • Do not restart/rechallenge subject with study treatment unless allowed per protocol and GSK Medical Governance approval is granted (refer to Appendix 6) • If restart/rechallenge not allowed per protocol or not granted, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow-up assessments **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase and bilirubin) and perform liver event follow-up assessments within 24 hrs • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline	• Viral hepatitis serology[1] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[3] • Blood sample for PK analysis, obtained 24-72 hrs after last dose[4] • Serum creatine phosphokinase and lactate dehydrogenase. • Fractionate bilirubin, if total bilirubin ≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE eCRF • Record use of concomitant medications on the concomitant medications eCRF including acetaminophen, herbal remedies, other OTC medications • Record alcohol use on the liver event alcohol intake eCRF **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins. • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen

Actions	Follow-Up Assessments
• A specialist or hepatology consultation is recommended For All other criteria: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within 24-72 hrs • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, MRI or CT) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRFs

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; DNA, deoxyribonucleic acid; eCRF, electronic case report form; GSK, GlaxoSmithKline; HPLC, high performance liquid chromatography; hrs, hours; IgG/IgM, immunoglobulin G or M; INR, international normalization ratio; MRI, magnetic resonance imaging; OTC, over-the-counter; PCR, polymerase chain reaction; PK, pharmacokinetic; RNA, ribonucleic acid; SAE, serious adverse event; SRM, Study Reference Manual; ULN, upper limit of normal

1. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
2. All events of ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
4. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.

Table 9 Liver Chemistry Increased Monitoring Criteria with Continued Therapy

Criteria	Actions
Subject with entry criteria ALT≤2.5xULN ALT ≥3xULN but <5xULN and bilirubin <2xULN, without symptoms believed to be related to liver injury or hypersensitivity and who can be monitored weekly for 4 weeks Subject with documented liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5xULN but ≤5xULN ALT ≥3xULN and 1.5x baseline value but ALT <5xULN and 2x baseline value and bilirubin <2xULN, without symptoms believed to be related to liver injury, or hypersensitivity and who can be monitored weekly for 4 weeks	• Notify the GSK Medical Monitor within 24 hrs of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above For subjects with entry criteria ALT≤2.5xULN • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline. For subjects with documented liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5xULN but ≤5xULN • If, after 4 weeks of monitoring, ALT <3xULN and <1.5x baseline value, and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GSK, GlaxoSmithKline; hrs, hours; ULN, upper limit of normal

Refer to Appendix 6 for liver safety drug restart or rechallenge guidelines.

Section 7.2.3 Events Associated with GSK2636771 – renamed Left Ventricular Ejection Fraction (LVEF) Stopping Criteria

NEW TEXT

Echocardiography (or multigated acquisition [MUGA] scan) must be performed at Screening and as clinically indicated as outlined in the Time and Events Tables (Section 8.1). Subjects who have an absolute decrease of >10% in LVEF compared with baseline and the ejection fraction is below the institution's lower limit of normal (LLN) should temporarily discontinue treatment with GSK2636771 and have a repeat evaluation of LVEF within 1 week. Echocardiogram or MUGA should be repeated every 1 to 2 weeks for 4 weeks or until LVEF recovery to above institutional LLN and within 10% of baseline.

- **If the LVEF recovers (defined as ≥LLN and absolute decrease ≤10% compared with baseline) at any time during the next 4 weeks, after consultation and approval of the GSK Medical Monitor, the subject may be restarted on GSK2636771 at a reduced dose. For such subjects, monitoring of LVEF will be performed 2 and 4 weeks after re-challenge, and every 4 weeks thereafter for a total of 16 weeks and then per protocol.**
- **If repeat LVEF does not recover within 4 weeks, treatment with GSK2636771 should be permanently discontinued. Ejection fraction should be monitored every 4 weeks for a total of 16 weeks or until resolution.**

Subjects with Grade 3 or 4 (symptomatic) left ventricular systolic dysfunction must discontinue treatment with GSK2636771. Ejection fraction should be monitored every 4 weeks for a total of 16 weeks or until resolution. If recovery occurs (LVEF >institutional LLN and symptom resolution) within 4 weeks, treatment with GSK2636771 may be restarted at a reduce dose in consultation with the GSK Medical Monitor.

Copies of all ECHOs (or MUGA scans) and cardiology consultations performed on subjects who experience a >10% decrease in LVEF from baseline and whose cardiac ejection fraction is <institution's LLN will be required by GSK for review. Instructions for submitting qualifying ECHOs (or MUGA scans) are provided in the SRM.

Section 7.2.4 Valvular Toxicity Stopping Criteria (NEW SECTION)

NEW TEXT

Subjects who have a new asymptomatic, moderate regurgitation or stenosis by ECHO or MUGA scan (Grade 2 mitral/tricuspid/aortic valvular toxicity per CTCAE v4.0 should temporarily discontinue treatment with GSK2636771 and have a repeat evaluation by ECHO within 1 week. An ECHO (or MUGA scan) should be repeated every 1 to 2 weeks for 4 weeks or until valve recovery to baseline.

- **If the valve recovers to baseline any time during the next 4 weeks after consultation and approval of the GSK Medical Monitor, the subject may be restarted on GSK2636771 at a reduced dose(s). For such subjects, monitoring of the valve via ECHO (or MUGA scan) will then be performed 2 and 4 weeks after re-challenge, and every 4 weeks thereafter for 8 weeks and then per protocol.**
- **If repeat ECHO (or MUGA scan) does not reveal valve recovery to baseline within 4 weeks, then the subject should permanently discontinue GSK2636771. The valve should continue to be monitored via ECHO (or MUGA scan) every 4 weeks for 8 weeks or until resolution.**

Subjects with a Grade 3 or 4 (symptomatic, severe regurgitation/stenosis by imaging with symptoms controlled by medical intervention) valvular toxicity must discontinue GSK2636771. Valvular toxicity should continue to be monitored every 4 weeks for 8 weeks or until resolution. If recovery occurs (return to baseline via

imaging AND symptom resolution) within 4 weeks, the subject may restart GSK2636771 at a reduced dose after consultation and approval of the GSK Medical Monitor.

ECHO (or MUGA scan) must be performed within 28 days of Day -1 and at the End of Study visit (see Time and Events Tables in Section 8.1). Copies of all ECHO(s) (or MUGA scan) and cardiology consultations performed on subjects who experience valvular toxicity will be required by GSK for review. Instructions for submitting qualifying ECHOs (or MUGA scans) are provided in the SRM.

Section 7.3 Management Guidelines for Specific Events Associated with GSK2636771 (NEW SECTION)

NEW TEXT

If a subject experiences an AE during the Enzalutamide Run-In Period resulting in a dose interruption that precludes the subject from completing the run-in period within 14 days or a dose reduction, the GSK Medical Monitor should be contacted as approval will be required in order for the subject to continue in the study (refer to the SRM).

Section 7.3.1 Renal Insufficiency or Other Renal Events – Table 10

REVISED TEXT

Table 10 Management and Dose Modification of Renal Events

Assessment	Action and Dose Modification
Urine dipstick protein ≥2+	• Monitor for concomitant medications (e.g., NSAIDs) or medical conditions (e.g., menstruation, urinary tract infection) associated with positive urinary protein dipstick test (see SRM for further details) • Assess BP and ensure it is well-controlled (<140/90 mmHg) • Obtain a random UPC ratio (**see Appendix 5**)

Serum creatinine ≥0.5 mg/dL (≥44.2 µmol/L) increase from baseline	• Repeat serum creatinine level within 24 hrs of previous result
	• If repeat value confirms serum creatinine ≥0.5 mg/dL (≥44.2 µmol/L) increase from baseline:
	  • Immediately interrupt treatment with GSK2636771
	  • Evaluate and treat possible causes for elevated serum creatinine (e.g., renal outflow obstruction, sepsis, dehydration, hypotension, GI bleed, medications [e.g., trimethoprim, ketoconazole or cimetidine] that increase serum creatinine level)
	  • **Obtain blood sample for PK analysis, if requested (see SRM), within 24-72 hrs after the last dose (refer to Section 8.7.3.1 for details on PK sample collection)**
	  • Consider oral or IV hydration, if clinically indicated
	  • Repeat serum creatinine level every 7 days or more frequently if clinically indicated

Assessment	Action and Dose Modification

	• If serum creatinine fails to improve (≥0.5 mg/dL [≥44.2 µmol/L] increase persists) within 14 days following dose interruption:
	  • Permanently discontinue treatment with GSK2636771
	  • Consult with GSK Medical Monitor
	• If serum creatinine improves (<0.5 mg/dL [<44.2 µmol/L] increase from baseline) within 14 days following dose interruption:
	  • Restart treatment with GSK2636771 with dose reduced by one dose level
	  • Repeat serum creatinine level every 4 weeks or more frequently if clinically indicated
	• If elevated serum creatinine recurs after one dose reduction (≥0.5 mg/dL [≥44.2 µmol/L] increase from baseline):
	  • Repeat serum creatinine within 24 hrs to confirm result
	  • If repeat serum creatinine confirms increase, withdraw subject from treatment/study unless there is agreement between investigator and GSK Medical Monitor that subject will benefit from continued treatment following recovery of serum creatinine (≤0.5 mg/dL [<44.2 µmol/L] increase from baseline)
	  • If repeat serum creatinine fails to confirm increase, continue treatment with GSK2636771 at same dose level without interruption

Hypocalcemia (serum calcium ≥Grade 2) or Hypophosphatemia (serum phosphate ≥Grade 3 or symptomatic Grade 2)	• Repeat serum calcium or phosphate level within 24 hrs of previous result
	  • If repeat value confirms Grade 2 serum calcium, or symptomatic Grade 2 serum phosphate.
	  • Immediately interrupt treatment with GSK2636771
	  • Treat as clinically indicated by local institutional standards
	  • **Obtain serum PTH level**
	  • **Obtain blood sample for PK analysis, if requested (see SRM), within 24-72 hrs after the last dose (refer to Section 8.7.3.1 for details on PK sample collection)**
	  • Obtain urine samples for urine creatinine, calcium, phosphate, and protein at treatment interruption; repeat every 7 days
	  • Repeat serum calcium or phosphate level every 7 days or more frequently if clinically indicated
	• If serum calcium fails to improve to Grade 1 or if serum phosphate fails to improve to asymptomatic Grade 2 within 14 days following dose interruption:
	  • Permanently discontinue treatment with GSK2636771
	  • Consult with GSK Medical Monitor
	• If serum calcium improves to Grade 1 or serum phosphate improves to asymptomatic Grade 2 or baseline, whichever is more improved within 14 days following dose interruption:
	  • Restart treatment with GSK2636771 with dose reduced by one dose level
	  • Repeat serum calcium or phosphate level per Time and Events Tables (Section 8.1) or more frequently if clinically indicated
	• If decreased serum calcium or phosphate levels reoccurs after one dose reduction :

Assessment	Action and Dose Modification
	• Repeat serum calcium or phosphate levels within 24 hrs to confirm result • If repeat serum calcium or phosphate levels confirm decrease, withdraw subject from treatment/study unless there is agreement between investigator and GSK Medical Monitor that subject will benefit from continued treatment following recovery of serum calcium or phosphate to baseline with dose of GSK2636771 further reduced one dose level. • If repeat serum calcium or phosphate fails to confirm a decrease, continue treatment with GSK2636771 at same dose level without interruption

Abbreviations: BP, blood pressure; GI, gastrointestinal; GSK, GlaxoSmithKline; IV, intravenous; mmHg, millimeters of mercury; NSAIDs, non-steroidal anti-inflammatory drugs; **PK, pharmacokinetics**; **PTH, parathyroid hormone**; RBC, red blood cell; SRM, Study Reference Manual; UPC, urine/protein/creatinine ratio

Section 7.3.1.1. (New Section)

NEW TEXT

Serum parathyroid hormone (PTH) level will be assessed on the first day of combination treatment (Week 1, Day 1 of Combination Treatment Period). Subsequently a serum PTH level should be obtained for any subject who experiences Grade 2 or greater hypocalcemia or hypophosphatemia while on study (refer to Table 10).

Section 7.3.2 Cardiac-related Toxicities

REVISED TEXT

Reversible increases in mean arterial pressure **and** decreases in heart rate and cardiac contractility that were considered secondary to an elevation in blood pressure were observed in a single dose safety pharmacology study in dogs **administered 300 mg/kg of GSK2636771.** In the ongoing FTIH study, no Grade 3 or higher cardiac events have been observed. Subjects with a history of uncontrolled hypertension, heart failure, or known significant coronary artery disease are excluded from this study. Cardiac monitoring, including assessment of blood pressure and heart rate, along with 12-lead ECGs, will be performed.

Section 7.3.2.1 Hypertension

REVISED TEXT

Table 6 Management and Dose Modification for Hypertension

Section 7.3.3 Rash

REVISED TEXT

Table 7 Management and Dose Modification for Rash

Section 7.3.4 Diarrhea (NEW SECTION)

NEW TEXT

Episodes of diarrhea have occurred in subjects receiving GSK2636771 monotherapy. Other frequent causes for diarrhea, including concomitant medications (e.g., stool softeners, laxatives, antacids, etc.), infections by *C. difficile* or other pathogens, partial bowel obstruction, should be clinically excluded.

Standardized and universal guidelines have been developed by an American Society of Clinical Oncology (ASCO) panel for treating chemotherapy-induced diarrhea [Benson, 2004]. Presented in the sections below are the recommended guidelines for the management of diarrhea in subjects receiving GSK2636771. These guidelines were derived from the recommendations published by the ASCO panel [Benson, 2004].

Early identification and intervention is critical for the optimal management of diarrhea. A subject's baseline bowel patterns should be established so that changes in patterns can be identified while subject is on treatment.

An assessment of frequency, consistency and duration as well as knowledge of other symptoms such as fever, cramping, pain, nausea, vomiting, dizziness and thirst should be taken at baseline. Consequently subjects at high risk of diarrhea can be identified. Subjects should be educated on signs and symptoms of diarrhea with instructions to report any changes in bowel patterns to the physician.

It is recommended that subjects keep a diary and record the number of diarrhea episodes and its characteristics. They should also include information on any dietary changes or other observations that may be useful in the evaluation of their diarrhea history.

If subjects present with diarrhea of any grade, check they are receiving the study treatment correctly (i.e., single dose, rather than splitting it through the day). Obtain information on food (solid and liquid) and over-the-counter (OTC) medication(s), including herbal supplements, taken during the treatment period.

Guidelines regarding management and dose reduction for diarrhea considered to be related to study treatments by the investigator are provided in Table 13.

Table 13 Management and Dose Modification Guidelines for Diarrhea

Grade	Management	Action and Dose Modification
Uncomplicated Diarrhea - Grade 1	1. Instruct subject to start supportive care immediately at the first episode of diarrhea (i.e., unformed stool) and contact the investigator. • Administer loperamide: Initial dose: 4 mg. Subsequent doses: 2 mg after each unformed stool 19. Re-evaluate after 24 hrs: 20. *If diarrhea is resolving:* continue loperamide treatment at 2 mg dose after each unformed stool until diarrhea-free (i.e., bowel patterns return to baseline) for 12 hrs. If diarrhea recurs, re-initiate loperamide as needed to maintain normal bowel pattern. 21. *If diarrhea is NOT resolving:* continue loperamide 2 mg every 4 hrs for the next 24 hrs; re-evaluate after 24 hrs. If not resolving, administer loperamide 2 mg after each unformed stool until diarrhea free (i.e., bowel patterns return to baseline) for 12 hrs. If diarrhea is not resolving, continue loperamide 2 mg every 4 hrs and re-evaluate every 24 hrs. 2. Dietary modifications: 22. Stop all lactose containing products and eat small meals 23. Avoid spicy, fried and fatty foods, raw vegetables and other foods high in fiber 24. Avoid caffeine and alcohol (can irritate bowel and increase motility) 25. Hydration: Drink 8 to 10 large glasses of clear liquids (e.g., water, electrolyte drink) daily. Avoid acidic drinks such as tomato juice and fizzy soft drinks 26. Supplement diet to include food rich in potassium (e.g., bananas, potatoes, apricots; evaluate their impact on diarrhea due to fiber content (e.g., apricots)	• Continue study treatments at current dose. • Continue supportive care until diarrhea resolves (diarrhea free for 12 hrs and bowel pattern returns to baseline) • If diarrhea recurs after stopping loperamide treatment, resume loperamide treatment, re-introduce diet modifications, and continue study treatments at current dose.
	3. If Grade 1 diarrhea persists for >1 week with loperamide treatment, consider treatment with second-line agents (i.e., octreotide,	

Grade	Management	Action and Dose Modification
	budesonide or tincture of opium). 4. If Grade 1 diarrhea persists for ≥2 weeks, refer to Persistent Grade 2 diarrhea management guidelines.	
Uncomplicated Diarrhea – Grade 2	1. Instruct subject to start supportive care immediately at the first episode of diarrhea (i.e., unformed stool) and contact the investigator. 27. Administer loperamide: Initial dose: 4 mg. Subsequent doses: 2 mg every 4 hrs or after each unformed stool 28. Re-evaluate after 24 hrs: 29. *If diarrhea is resolving:* continue loperamide treatment at 2 mg dose after each unformed stool until diarrhea free (i.e., bowel patterns return to baseline) for 12 hrs. If diarrhea recurs, re-initiate loperamide as needed to maintain normal bowel pattern. 30. *If diarrhea is NOT resolving:* consider loperamide 2 mg every 2 hrs for the next 24 hrs. If Grade 2 diarrhea persists after 48 hrs of loperamide treatment, start treatment with second-line agents (i.e., octreotide, budesonide or tincture of opium). Consider performing stool work-up, CBC, electrolytes and other tests as appropriate. 2. Dietary modifications: 31. Stop all lactose containing products and eat small meals 32. Avoid spicy, fried and fatty foods, bran, raw vegetables and other foods high in fiber. Eat foods low in fiber (i.e., lean meat, rice, skinless chicken or turkey, fish, eggs, canned or cooked skinless fruits, cooked/pureed vegetables) 33. Avoid caffeine and alcohol (can irritate bowel and increase motility) 34. Hydration: Drink 8 to 10 large glasses of clear liquids (e.g., water, electrolyte drink) daily. Avoid acidic drinks such as tomato juice and fizzy soft drinks	• Continue study treatments at current dose. • Continue supportive care until diarrhea resolves (diarrhea free for 12 hrs / bowel pattern returns to baseline) • Once diarrhea has resolved, subject may gradually re-introduce foods from their normal diet. • If diarrhea recurs after stopping loperamide treatment, resume loperamide treatment, re-introduce diet modifications, and continue study treatments at current dose.

Grade	Management	Action and Dose Modification
	35. Supplement diet to include food rich in potassium (e.g., bananas, potatoes, apricots); evaluate their impact on diarrhea due to fiber content (e.g., apricots) 36. If diarrhea recurs, refer to Recurrent Diarrhea management guidelines.	
Persistent (≥3 days/ 72 hrs) Diarrhea – Grade 2	1. If Grade 2 diarrhea persists for ≥3 days or 72 hrs, resume loperamide treatment and re-introduce diet modifications. 2. If supportive care measures and interruption of study treatments are ineffective in treatment of persistent Grade 2 diarrhea, perform stool work-up, CBC, electrolytes, and other tests as appropriate. Consider consultation with GI specialist.	• Hold treatment with GSK2636771 and enzalutamide until symptoms have resolved to Grade 1 or baseline bowel pattern. • Once diarrhea has resolved, continue treatment with GSK2636771 and enzalutamide at reduced dose.
Recurrent Diarrhea (>1 occurrence) - (Grade 2)	If second occurrence of Grade 2 diarrhea recurs, resume loperamide treatment and re-introduce diet modifications.	• Once diarrhea resolves to Grade 1 or baseline, consider re-starting study treatments (GSK2636771 + enzalutamide) at a reduced dose
Complicated Diarrhea[2] – Grade 3 or Grade 1 or 2 with complicating factors	1. Instruct subject that they must call investigator immediately for any complicated severe diarrhea event. 2. If loperamide has not been initiated, initiate loperamide immediately. Initial dose: 4 mg. Subsequent doses: 2 mg every 2 hrs or after each unformed stool. 3. Refer to the dietary modifications for Grade 1 and 2 uncomplicated diarrhea (above). 4. For dehydration use IV fluids as appropriate. If subject presents with severe dehydration, administer octreotide. 5. Perform stool work-up, complete blood count, electrolytes and other tests as appropriate 6. Administer antibiotics (i.e., fluoroquinolones) as needed, especially if diarrhea is persistent beyond 24 hrs or if fever or Grade 3 or 4 neutropenia is present 7. Intervention may require hospitalization for subjects most at risk for life threatening	• Hold treatment with GSK2636771 and enzalutamide until symptoms have resolved to Grade 1 or baseline bowel pattern and without complicating factors present. • Once diarrhea resolves to Grade 1 or baseline, consider re-starting study treatments (GSK2636771 +enzalutamide) at a reduced dose • Continue supportive care until diarrhea resolves (diarrhea free for 24 hrs and bowel pattern returns to baseline)

Grade	Management	Action and Dose Modification
	complications.	
Complicated Diarrhea – Grade 4	1. Instruct subject that they must call investigator immediately for any complicated Grade 4 diarrhea event. 2. If loperamide has not been initiated, initiate loperamide immediately. Initial dose: 4 mg. Subsequent doses: 2 mg every 2 hrs or after each unformed stool. 3. For dehydration use IV fluids as appropriate. If subject presents with severe dehydration, administer octreotide. 4. Perform stool work-up, CBC, electrolytes and other tests as appropriate 5. Consider consultation with GI specialist. 6. Administer antibiotics (i.e., fluoroquinolones) as needed, especially if diarrhea is persistent beyond 24 hrs or if fever or Grade 3 or 4 neutropenia is present 7. Intervention may require hospitalization for subjects most at risk for life threatening complications.	• Hold treatment with GSK2636771 and enzalutamide • Consult with GSK Medical Monitor to discuss subject's event history, re-initiation of study treatments, and dose modifications, once symptoms have resolved to Grade 1 or baseline bowel pattern • Continue supportive care until diarrhea resolves (diarrhea free for 24 hrs and bowel pattern returns to baseline)

Abbreviations: CBC, complete blood count; GI, gastrointestinal; hrs, hours; IV, intravenous; mg, milligram(s)

Section 7.3.5 Vomiting (NEW SECTION)

NEW TEXT

Table 14 Management and Dose Modification for Events of Vomiting

Grade	Action and Dose Modification
≤Grade 1	Continue study treatments at current dose.
Grade 2	Hold until ≤Grade 1. Resume study treatments at same dose level.
Grade 3	Hold[1] until <Grade 2. Resume study treatments at one dose level lower, if indicated.[2]
Grade 4	Withdraw study treatments.

[1]Subjects requiring a delay of >14 days should be withdrawn from treatment and/or study.
[2]Subjects requiring >2 dose reductions should be withdrawn from treatment and/or study.

It is recommended that any event of vomiting should be managed with the use of antiemetics.

Section 8.2.1 Consent for Pre-Screening

REVISED TEXT

The subject will be asked to provide written informed consent for pre-screening **prior to any of the** ~~he investigator or other designated study personnel will determine if the subject is eligible for pre-screening by reviewing the eligibility criteria and completing all of The~~ pre-screening assessments outlined in the Time and Events Tables (Section 8.1) **are performed.**

Section 8.2.2 Consent for Screening

REVISED TEXT

If**, during pre-screening,** the subject is determined ~~during pre-screening~~ to have a PTEN deficient tumor, the subject will be asked to provide written informed consent **prior to screening for** enrollment in the study. The investigator or other designated study personnel will determine if the subject is eligible for enrollment in the study by reviewing the eligibility criteria and completing all of the Screening assessments outlined in the applicable Time and Events Tables in Section 8.1.

Section 8.3.1 Pre-Screening: Determination of PTEN Deficiency Status, 2nd paragraph

REVISED TEXT

After written informed consent is provided by the subject archived tissue will be submitted to determinethe PTEN deficiency status of the subject's tumor. If archived tumor tissue is not available, fresh tumor tissue should be obtained by **pre-treatment** biopsy to determine PTEN deficiency. The PTEN testing will be performed at a GSK selected laboratory and the tumor specimen should be provided to that laboratory. The PTEN status will be communicated to sites by GSK authorized personnel.

Section 8.3.2 Screening

REVISED TEXT

Subjects **with confirmed PTEN deficiency and** ~~who~~ **have** provide written informed consent for screening will be eligible to undergo specific screening assessments to determine eligibility for the study.

Section 8.4 Demographics and Medical History

REVISED TEXT

Demographic data will include gender, ~~date~~ **year** of birth, ~~race,~~ height, weight, ethnicity and geographic ancestry.

Medical, surgical, and treatment history including date ~~(month and year)~~ of first diagnosis, histology, current sites of disease as well as cardiovascular risk factors, alcohol

and tobacco history, plus family history will be taken as part of the medical history and disease status.

Section 8.6 Safety

REVISED TEXT

Measurements used to evaluate safety will include physical examinations, vital sign (BP, temperature and ~~pulse~~ **heart** rate) measurements, ECOG performance status, 12-lead ECGs, ECHO/MUGA, clinical laboratory tests and monitoring for AEs. Planned time points for all safety assessments are listed in the applicable Time and Events Tables (Section 8.1).

Section 8.6.2 Vital Signs

REVISED TEXT

Vital sign measurements will include BP, temperature, and ~~pulse~~**heart** rate. Vital signs may be measured as indicated in the Time and Event Tables (Section 8.1) or more frequently if warranted by clinical condition of the subject. Refer to the SRM for details regarding measurement of vital signs.

Section 8.6.5 Echocardiogram and/or Multi-gated Acquisition (MUGA) Scans (NEW SECTION)

NEW TEXT

Echocardiograms (ECHOs) or MUGA scans will be performed at baseline to assess cardiac ejection fraction and cardiac valve morphology for the purpose of study eligibility, as specified in the Time and Events Tables (Section 8.1). Additional ECHO assessments may be performed if clinically warranted. The evaluation of the echocardiographer should include an evaluation for LVEF and both right and left-sided valvular lesions.

Copies of all ECHOs or MUGA scans performed on subjects who experience an absolute decrease >10% in LVEF compared to baseline concurrent with LVEF < institutional LLN may be required by GSK for review.

Refer to the SRM for further details on submission of ECHOs or MUGA scans.

Section 8.6.6. Laboratory Assessments, 1st, 2nd, 3rd paragraphs

REVISED TEXT

Laboratory tests may be done up to 24 hrs prior to the scheduled visit. Laboratory test results are to be reviewed prior to administration of ~~the first dose of~~ study treatment.

Liver function tests and urine tests for **UPC** ~~protein/creatinine~~ may be performed up to 72 hrs prior to the scheduled visit in order to have results available for review by investigator prior to the scheduled visit date.

Any laboratory test with a value outside the normal range may be repeated **during Screening** ~~(prior to the first dose)~~ at the discretion of the investigator. A subject with a laboratory value outside the reference range(s) may be included only if the investigator and GSK Medical Monitor agree that it is unlikely to introduce additional risk factors and will not interfere with study procedures.

Table 17 Laboratory Assessments

Other tests
PSA
Serum Testosterone
Coagulation Tests: PT/PTT/INR
Serum Parathyroid Hormone (PTH)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; INR, international normalization ratio; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; PSA, prostate-specific antigen; PT, prothrombin time; **PTH, parathyroid hormone**; PTT, partial thromboplastin time; RBC, red blood cell; ULN, upper limit of normal; UPC, urine/protein/creatinine ratio; WBC, white blood cell

1. Direct bilirubin is required only if the total bilirubin is elevated (≥2 times ULN)
2. Chemistry evaluation of chloride or uric acid is not required where there are logistical constraints.
3. See Appendix 5

Section 8.7.1 PK Assessments: Dose Escalation Phase

REVISED TEXT

~~Blood~~ **Plasma** samples for PK analysis **of enzalutamide and N-desmethyl enzalutamide** will be collected from all subjects **on Day 14 of the Enzalutamide Run-In Period. Blood and plasma samples for the analysis of GSK2636771, enzalutamide, and N-desmethyl enzalutamide will be collected from all subjects on Week 5, Day 29 and during Weeks 8 and 12 of the Treatment Continuation Period. These PK samples will be collected** to evaluate if there is an effect of GSK2636771 on the PK of enzalutamide and to quantify the systemic exposure to GSK2636771, **enzalutamide and N-desmethyl enzalutamide.**

Section 8.7.2 PK Assessments: Dose Expansion Phase

REVISED TEXT

A ~~sparse~~ **reduced** PK sampling strategy will be used for subjects in the Dose Expansion Phase **(on Day 29, Week 5 and during Weeks 8 and 12)** to quantify the systemic exposure to ~~study treatments~~ **GSK2636771, enzalutamide and N-desmethyl enzalutamide.**

Section 8.7.3 PK Blood Sample Collection

REVISED TEXT

~~Serial~~ **B**lood **and/or plasma** samples for PK analysis of GSK2636771 **and/or** enzalutamide and N-desmethyl enzalutamide will be collected at the time points indicated

in the Time and Events Tables (see Section 8.1). Whenever possible, blood for PK samples should be drawn from the peripheral arm vein or from a central IV port. Each PK sample should be collected as close as possible to the planned time relative to the dose (i.e., time zero) administered to the subject on serial PK days. Once preliminary PK data have been reviewed, the planned sample collection times or study day may be revised based on newly available data (i.e., to obtain data closer to the time of peak plasma concentration) to ensure appropriate monitoring. These changes must be approved and documented by GSK, but will not constitute a protocol amendment.

For Dose-Escalation Phase: ~~Blood samples for analysis of enzalutamide and N-desmethyl enzalutamide will be collected pre-dose and 0.5, 1, 2, 3, 4, and 6 hrs post-dose on the day prior to administration of the first dose of GSK2636771 (Day -1).~~

~~Blood samples for the analysis of GSK2636771 + enzalutamide should be collected on Day 29 at pre-dose and 0.5, 1, 2, 3, 4, and 6 hrs post-dose~~**. Blood and/or plasma samples for analysis of GSK2636771 and/or enzalutamide and N-desmethyl enzalutamide will be collected according to a serial sampling scheme in the Dose Escalation Phase.**

- **Day 14 (Enzalutamide Run-In Period): the day prior to administration of the first dose of GSK2636771: Subjects will be instructed to fast overnight (at least 8 hrs) and withhold their dose of enzalutamide prior to the study visit on Day 14. Study treatments will be administered in the clinic after the pre-dose blood draw is completed. Subjects will continue to fast for 2 hrs post-dose. Plasma samples for analysis of enzalutamide and N-desmethyl enzalutamide will be collected pre-dose and 0.5, 1, 2, 3, 4, and 6 hrs post-dose of enzalutamide (total of 7 samples).**

- **Day 29, Week 5 (Treatment Continuation Period): Subjects will be instructed to fast overnight (at least 8 hrs) and withhold the doses of study treatment prior to the study visit. Study treatments will be administered in the clinic after the pre-dose blood draws are completed. Subjects will continue to fast for 2 hrs post-dose. Blood and plasma samples for the analysis of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be collected at pre-dose and 0.5, 1, 2, 3, 4, and 6 hrs post-dose (total of 14 samples).**

- **Weeks 8 and 12 (Treatment Continuation Period): Subjects will be instructed to withhold the doses of study treatment prior to the study visit (no overnight fast is necessary). Study treatments will be administered in the clinic after the pre-dose blood draws are completed, either 1 hr before or 2 hrs after a meal. Blood and plasma samples for the analysis of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be collected pre-dose only (total of 2 samples per visit).**

For Dose Expansion Phase: ~~Blood samples for analysis of enzalutamide and N-desmethyl enzalutamide will be collected according to a sparse sampling scheme in subjects in the Dose Expansion Phase. Subjects with morning clinic visits will be instructed to withhold the doses of study treatment prior to the Week 5 visit. A pre-dose~~

~~blood sample for analysis of enzalutamide, N-desmethyl enzalutamide, and GSK2636771 will be collected prior to administration of study treatment at the clinic. Additional blood samples for analysis of enzalutamide, N-desmethyl enzalutamide, and GSK2636771 will be collected 1, 2, and 3 hrs post-dose. Subjects with afternoon clinic visits will take study treatments at the usual time. Blood samples for analysis of enzalutamide, N-desmethyl enzalutamide, and GSK2636771 will be collected at approximately 5 to 6, 6 to 7, and 7 to 8 hrs after administration of study treatments.~~ **Blood and plasma samples for analysis of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be collected according to a sparse sampling scheme in the Dose Expansion Phase. Overnight fast is not necessary for any of these PK days. Study treatments should be administered either 1 hr before or 2 hrs after a meal.**

- **Day 29, Week 5 (Treatment Continuation Period):**
    - ***Subjects scheduled for a morning clinic visit*** **will be instructed to withhold the doses of study treatments prior to the study visit. Study treatments will be administered in the clinic after the pre-dose blood draws are completed (either 1 hr before or 2 hrs after a meal). Blood and plasma samples for analysis of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be collected at pre-dose and 1, 2, and 3 hrs post-dose (total of 8 samples).**
    - ***Subjects scheduled for an afternoon clinic visit*** **will take their doses of study treatments at the usual time in the morning (either 1 hr before or 2 hrs after a meal). Blood and plasma samples for analysis of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be collected approximately 5 to 6, 6 to 7, and 7 to 8 hrs post-dose (total of 6 samples).**
- **Weeks 8 and 12 (Treatment Continuation Period): Subjects will be instructed to withhold the doses of study treatments prior to the study visit. Study treatments will be administered in the clinic after the pre-dose blood draw is completed (either 1 hr before or 2 hrs after a meal). Blood and plasma samples for the analysis of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be collected pre-dose only (total of 2 samples per visit).**

Details of PK blood **and plasma** sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the SRM.

Section 8.7.3.1 Additional PK Blood Sample Collection

NEW TEXT

Blood and plasma samples for PK analysis will also be collected within 24-72 hrs after the last dose of study treatment(s) at the time of a treatment-emergent AE of special interest unless the event occurs on the same day that the Day 14 (Enzalutamide Run-In Period) and/or Week 5, Day 29 (Treatment Continuation Period) PK samples are obtained.

The date/time of the PK blood and plasma sample draw and the date/time of the last dose of study treatments prior to the PK blood and plasma sample draws will be recorded on the eCRF. If the date or time of the last dose of study treatment is unclear, provide the subject's best approximation. If the date/time of the last dose of study treatment cannot be approximated OR PK blood or plasma samples cannot be collected in the time period indicated above, do not obtain a PK samples. Refer to the SRM for instructions on sample handling and shipping of the PK samples.

Section 8.7.4 Pharmacokinetic Sample Analysis

REVISED TEXT

Blood and plasma analysis will be performed under the control of GSK Platform Technology and Science-Drug Metabolism and Pharmacokinetics (PTS-DMPK)/Scinovo, the details of which will be included in the SRM. Concentrations of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be determined in **blood and** plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once **the blood and** plasma has been analyzed for GSK2636771, enzalutamide and N-desmethyl enzalutamide any remaining **blood or** plasma may be analyzed for other compound-related metabolites and the results reported under a separate GSK PTS-DMPK protocol.

Section 8.7.5 Meals, Alcohol, Tobacco and Activity Restrictions

REVISED TEXT

Meals

~~On serial PK sampling days subjects will fast for 4 hrs before and 2 hrs after dosing of the study treatments.~~

Subjects will be instructed to take study treatments at least 1 hr before or 2 hrs after a meal unless otherwise instructed due to PK, CTC, and/or urine electrolyte sampling (see Section 6.3 for details).

Tobacco

~~Subjects who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit.~~

Smoking while in the clinical unit will not be permitted. Subjects who use tobacco products may use nicotine patches while they are in the clinical unit.

Section 8.8 Clinical Activity

NEW TEXT

Refer to the SRM for further details on submission of CT scans, MRIs and bone scans.

Section 8.9.1 Predictive Biomarkers, first paragraph

REVISED TEXT

For subjects entered in the study, additional slides of tumor tissue samples will be collected and submitted to the designated central laboratory for analysis once a subject has received their first dose of GSK2636771 on Week 1, Day 1 of the Combination Treatment Period. The remaining **tumor** tissue submitted for the PTEN testing may be utilized for ~~retrospective analysis as detailed below~~**predictive biomarker analysis**. ~~Additional archival or pre-dose biopsy tumor tissue samples will also be requested for the enrolled subjects to complete the intended analysis.~~ . **If additional tumor tissue is not available, no new biopsy procedure is required in order to obtain tumor tissue for predictive biomarker analysis.**

Genetic changes known to alter or regulate PTEN function including mutation, loss of heterozygosity (LOH), silencing due to promoter methylation may also be assessed. Additional proteins, DNA, RNA, or microRNA, related to activity of GSK2636771and enzalutamide or prostate cancer may also be analyzed. Any remaining tumor tissue may also be utilized to further develop a ~~PTEN~~ diagnostic assay.

Section 8.9.3 Circulating Tumor Cells

NEW TEXT

Additional blood samples will be collected at the time points indicated in the Time and Events Tables (Section 8.1) to isolate CTCs using an EPIC Biosciences platform. The isolated CTCs will be analyzed for AR variants or other protein markers and potential genomic alterations (e.g., PTEN allele loss, AR amplifications, etc.).

If subject withdraws consent for further treatment and data collection, all samples collected for the biomarker analysis at the time of withdrawal will still proceed for analysis to meet the intended objectives defined in this protocol.

Details on sample collection, processing, storage and shipping procedures for all blood and tissue samples are provided in the SRM.

Section 8.9.3.1 CTC Conversion Rate

REVISED TEXT

CTC enumeration will be performed at a central laboratory using the analytically valid CellSearch system (Veridex LLC). For subjects with baseline CTC counts of ≥5 cells per 7.5 mL of blood, a conversion is defined as a decline in the CTC count to <5 cells per

7.5 mL of blood. **Genetic analysis of CTCs may also be performed by other laboratories.**

Section 8.9.4 Circulating Free Tumor DNA and Soluble Markers

REVISED TEXT

~~Assessment of gene mutations in circulating free tumor DNA (cfDNA) and other soluble markers will be performed to better understand clonal evolution and other predictive circulating biomarkers. Soluble markers may include cytokines or other immune response markers. DNA analysis includes mutation analysis of genes implicated in the PI3K/Ras/Raf or AR pathway.~~

Tumor-specific cfDNA levels detected in plasma or serum have been found to correlate with increasing tumor burden and decline following therapy. Furthermore, cfDNA in cancer subjects can harbor many genetic alterations (mutations, microsatellite alterations, aberrant methylation), which are generally consistent with the tumor. Thus, tumor-specific circulating cfDNA has the potential to be a useful biomarker of therapeutic response as well as offering a less invasive blood based technique for identifying predictive biomarkers.

Plasma samples for **analysis of** cfDNA and soluble markers will be collected **at the time points provided in the Time and Events Tables in Section 8.1.**~~during Screening, at Week 4 (pre-dose) and at time of disease progression for soluble markers and DNA analysis for all subjects enrolled in the study (see Time and Event Tables in Section 8.1)~~.

Section 8.10 Appendix 8: Genetic Research

NEW TEXT

Information regarding genetic research is included in Appendix 8.

Section 9.5 Time Period and Frequency of Detecting AEs and SAEs

REVISED TEXT

2nd paragraph: AEs will be collected from the time the first dose of enzalutamide is administered on **Week 1, Day 1 of the Enzalutamide Run-In Phase** ~~14 during the Screening Period~~ until 30 days following discontinuation of study treatments regardless of initiation of a new cancer therapy or transfer to hospice.

Section 10 Concomitant Medications and Non-Drug Therapies

REVISED TEXT

Subjects will be asked to provide a complete list of prescription and **OTC** medications that have been taken within 4 weeks prior to Screening. **Subjects will be instructed to inform** the investigator **prior to starting** any new medication(s), including herbal ~~preparations~~ and OTC products, taken from the time of the first dose of ~~study treatment~~ **enzalutamide monotherapy on Day 1 of the Enzalutamide Run-In Period until the**

end of the study (i.e. through the ~~final~~ post-treatment follow-up visit). **Any concomitant medication(s), including OTC and herbal product(s), taken during the study will be recorded in the eCRF. At a minimum, the drug name, dose and the dates of administration are to be recorded.** Additionally, a complete list of all prior cancer therapies will be recorded in the eCRF.

Questions regarding concomitant medications should be directed to the GSK Medical Monitor for clarification.

If **future** changes to the list of permitted or prohibited medications are made as a result of emerging data, formal documentation will be provided to the investigative site by GSK. Any such changes will be communicated to the investigative sites in the form of a letter, **which should be stored in the study file**. ~~Sites may also refer to the SRM for updates regarding changes to the list of permitted or prohibited medications.~~

Section 10.1 Permitted Medications, 3rd and 4th paragraphs

REVISED TEXT

Steroids: Use of steroids is discouraged while subject is undergoing treatment on this study. However, ***s***teroids (up to a maximum of 10 mg of prednisone or equivalent) are permitted provided that the subject has been on a stable dose for at least 4 weeks prior to **enrollment**~~first dose of study treatments~~**.**

Anticoagulants: Prophylactic doses of anticoagulants (i.e., heparin, warfarin) are permitted provided that the subject meets the PTT/INR entry criteria (see Section 4.1.2) and INR is monitored in accordance with local institutional practice. Therapeutic doses of warfarin (defined as a dose resulting in INR >1.5) are prohibited within 14 days prior to first dose of ~~study treatments~~ **Day 1 of the Enzalutamide Run-In Period** through the post-treatment follow-up visit. Caution should be exercised if aspirin is used concomitantly with GSK2636771.

Section 10.2 Prohibited Medications and Non-Drug Therapies

DELETED TEXT

- AR antagonists (e.g., bicalutamide, flutamide, nilutamide)

Section 10.2.1.1 GSK2636771 as Perpetrator of Drug-Drug Interactions (section header added)

DELETED TEXT

~~A preliminary study suggested the potential of CYP3A4 inhibition; however, subsequent studies did not confirm this. Use of medications that have a narrow therapeutic index and are substrates of CYP3A4 should be avoided within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study treatment and for the duration of study treatment through the post-treatment follow-up visit.~~

~~Drug(s) that are strong inducers of CYPs and UGTs as they may decrease the concentration of GSK2636771 (see Table 11). CYP3A4 substrates with a narrow therapeutic index, strong inducers of CYP3A4 and UGTs, and anti-platelet agents to avoid include, but are not limited to, those listed in Table 11 below. Consider therapeutic substitutions for these medications.~~

NEW TEXT

A preliminary study suggested the potential of CYP3A4 inhibition by GSK2636771; however, subsequent studies using human recombinant CYP3A4 and pooled human liver microsomes did not confirm this at concentrations tested (up to 100 µM). The preliminary study indicated GSK2636771 did not inhibit CYP1A2, 2C8, 2C9, 2C19 and 2D6 at up to 25 µM (10.8 µg/mL), the risk is low but was not fully discharged at higher concentrations. Medications that have a narrow therapeutic index and are substrates of CYP3A4 should be used with caution within 7 days or 5 half-lives (whichever is longer) prior to the first dose of GSK2636771 (Week 1, Day 1 of the Combination Treatment Period) and for the duration of study treatment through the post-treatment follow-up visit (Table 18). Medications that have a narrow therapeutic index and are substrates of CYP1A2, CYP2C8, 2C9 and 2C19, CYP2D6 and CYP2B6 should be used with caution. GSK2636771 did not inhibit transporters OATP1B1, OATP1B3, BCRP and P-gp up to 23-30 µM in vitro. Due to high GSK2636771 concentrations (up to 100 µM) observed in the FTIH study (P3B115717), there is a risk for renal transporter inhibition; however, in vitro data to discharge this risk is pending. Therefore, medications that are sensitive substrates of renal transporters OAT and OCT2 should be used with caution when administered with GSK2636771 (example drugs are listed in Table 18).

Table 18 Drugs Potentially Affected by GSK2636771: ~~Avoid~~ Use with Caution

Drugs/Agents	Therapeutic Area
CYP3A4 Substrates	
dihydroergotamine, ergonovine, ergotamine, methylergonovine	Ergot derivatives
pimozide	Neuroleptic
bepridil, flecainide, lidocaine, mexilitine, amiodarone, quinidine, propafenone	Antiarrhythmics
tacrolimus, sirolimus	Immune modulators
quetiapine, risperidone, clozapine, atomoxetine	Miscellaneous
~~***CYP Inducers and/or UGT enzymes***~~	
~~rifamycin class agents (e.g., rifampin, rifabutin, rifapentine)~~	~~Antibiotics~~
~~carbamazepine, phenobarbital, phenytoin, s-mephenytoin~~	~~Antiepileptic drugs~~
Antiplatelet agents	
ticlopidine, prasugrel or ticagrelor	Antiplatelet
Renal Transporter (OAT, OCT2) Substrates	
methotrexate	**Antineoplastic**
dofetilde, pilsicainide, procainamide	**Antiarrhythmic**
metformin	**Antidiabetic**

Section 10.2.1.2 GSK2636771 as Victim of Drug-Drug Interactions (section header added)

REVISED TEXT

~~Based on pre-clinical and *in vitro* data, CYP enzymes do not appear to mediate the metabolism of GSK2636771. However, strong inhibitors or inducers of CYP enzymes should be used with caution in the case that they may alter the PK of GSK2636771 (Table 12).~~

~~Based on pre-clinical and in vitro data GSK2636771 is a substrate for UDP-glucuronosyltransferase (UGT) enzymes. Therefore, drugs that are inhibitors of UGT enzymes should be used with caution (Table 12).~~

Based on pre-clinical and *in vitro* data, GSK2636771 is an in vitro substrate for UDP-glucuronosyltransferase (UGT) enzymes, while CYP enzymes did not appear to be the major pathways for metabolism of GSK2636771. Therefore, drug(s) that are strong inhibitors or inducers of CYPs and UGTs may increase or decrease the concentration of GSK2636771. Medications that are strong inhibitor/inducers of CYP3A4 and UGTs, including, but not limited to, those listed in Table 19, should be used with caution. Consider therapeutic substitutions for these medications.

Table 19 Drugs that may Potentially Affect GSK2636771: Use with Caution

Generic Drug Name	Therapeutic Area
Inducers of UGT enzymes	
rifamycin class agents (e.g., rifampin, rifabutin, rifapentine)	Antibiotics
carbamazepine, phenobarbital, phenytoin, s-mephenytoin	Antiepileptic drugs
~~***CYP Inhibitors***~~	
~~clarithromycin, telithromycin, troleandomycin~~	~~Antibiotics~~
~~itraconazole, ketoconazole, posaconazole, voriconazole~~	~~Antifungals~~
~~nefazodone~~	~~Antidepressants~~
~~gemfibrozil~~	~~Hyperlipidemia~~
~~bosentan, mibefranil, conivaptan~~	~~Miscellaneous~~
~~cyclosporine~~	~~Immunosuppressive agents~~
Inhibitors of UGTenzymes ~~inhibitors~~	
fluconazole	Antifungal
cisapride, probenecid, ranitidine, cyclosporine, diflunisal, sertraline, valproic acid, atavaquone, methadone, methsuximide, olanzapine, retigabine	Miscellaneous

Caution is also recommended when GSK2636771 and aspirin are used concomitantly.

Section 10.2.2 Potential Drug Interactions with Enzalutamide

NEW TEXT

The following information is provided as an initial reference, however, please refer to the approved US FDA prescribing information [Xtandi, 2013] or the Xtandi Prescribing Information for the area where it is approved for the most current drug-drug interaction (DDI) information and contraindicated medications.

Section 11.1 Contraception Requirements

REVISED TEXT

Abstinence: Male subjects may also elect abstinence, defined as sexual inactivity consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Complete abstinence from sexual intercourse **must occur** for 14 days prior to first dose of ~~study treatment~~ **enzalutamide monotherapy on Day 1 of the Enzalutamide Run-In Period**, through the dosing period, and until 3 months after the last dose of study treatments.

Sperm Donation: Subjects must not donate sperm from the ~~time~~ **day** of the first dose of ~~study treatment~~ **enzalutamide monotherapy on Day 1 of the Enzaluatmide Run-In Period** through 3 months after the last dose of study treatments.

Section 13.3.4.3 Pharmacokinetic Analyses

REVISED TEXT

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling and Simulation Department, GSK. Statistical analyses of the PK parameter data will be the responsibility of GSK Discovery Biometrics **and Clinical Statistics.**

~~Non-compartmental analysis will be conducted on~~ Concentration-time data **for GSK2636771, enzalutamide and N-desmethyl enzalutamide** from the Dose-Escalation Phase **will be analyzed via standard non-compartmental methods**. Parameters calculated include the area under the concentration-time curve from 0 to the last quantifiable blood or plasma concentration (AUC(0-t)), the maximum plasma or blood concentration (Cmax), and the time of the maximum concentration (tmax) if data permit. Population PK parameters **for GSK2636771** including oral clearance (CL/F), oral volume of distribution (V/F), and absorption rate constant (ka) will be estimated pooling all data from this study **with historical data**, if data permit. Dependent on the final structural PK model, additional PK parameters may also be estimated. Sources of variability in PK parameters will be investigated during population modeling.

Section 14.2 Regulatory and Ethical Considerations, Including the Informed Consent Process

NEW TEXT

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments, e.g. genetic research described in Appendix 7, unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

Section 16.1 Appendix 1: ECOG Performance Status

REVISED TEXT

5 Death

Section 16.4 Appendix 4: Disease Assessment per RECIST 1.1

NEW TEXT

Assessment Guidelines – CT and MRI:

NOTE: If CT contrast is contraindicated, acquire and submit a contrast-enhanced MRI of the abdomen/pelvis and an unenhanced CT of the chest in place of the enhanced CT for complete lesion assessment.

REVISED TEXT

Baseline Assessments – CT and MRI:

NOTE: Although CT scan is preferred, MRI may be used as an alternative method of baseline disease assessment **for abdomen/pelvis**, especially for those subjects where a CT scan is contraindicated due to allergy to contrast, provided that the method used to document baseline status is used consistently throughout study treatment to facilitate direct comparison. **An unenhanced CT of the chest can replace the enhanced CT of the chest, but MRI of the chest is not recommended.**

Confirmation of CR and PR are required per protocol. Confirmation assessments must be performed no less than 4 weeks **(±3 days)** after the criteria for response have initially been met and may be performed at the next protocol scheduled assessment. If a confirmation assessment is performed prior to the next protocol schedule assessment, the next protocol scheduled evaluation is still required (e.g. evaluations must occur at each protocol scheduled time point regardless of unscheduled assessments).

Baseline Assessments

The following baseline disease (lesion) assessments must be performed within 28 days ~~prior to enrollment~~ (or within 35 days if disease assessment is assessed by MRI) **prior to**

the first dose of enzalutamide (Day 1 of Enzalutamide Run-In Period) to identify target and non-target lesions:

Baseline documentation of target and non-target lesions

- All baseline lesion assessments must be performed within 28 days ~~prior to enrollment (~~or within 35 days if disease assessment is assessed by MRI) **prior to the first dose of enzalutamide (Day 1 of Enzalutamide Run-In Period)**.

Confirmation Criteria:

To be assigned a status of PR or CR, a confirmatory disease assessment should be performed no less than 4 weeks **(±3 days)** after the criteria for response are first met.

Confirmation of Response per RECIST 1.1

Confirmation of CR and PR are required per protocol. Confirmation assessments must be performed at least 4 weeks **(±3 days)** after the criteria for response have initially been met and may be performed at the next protocol scheduled assessment. If a confirmation assessment is performed prior to the next protocol-specified assessment, the next protocol-specified evaluation is still required (e.g., evaluations must occur at each protocol scheduled time point regardless of unscheduled assessments).

Brain metastases: To confirm a CR in a solid tumor subject with brain metastases at baseline, brain imaging that is obtained before the response assessment indicating a CR must have been obtained no earlier than 1 week prior to that response assessment imaging. Alternatively, brain imaging performed after a response assessment imaging suggesting a CR in a solid tumor subject with brain metastases must be done no more than 4 weeks **(±3 days)** after the next protocol specified assessment in order to confirm a CR.

Section 16.6 Appendix 6: Liver Safety Required Actions and Follow-up Assessments (Section deleted; subsequent sections renumbered)

DELETED TEXT

~~**Phase I liver chemistry stopping and increased monitoring criteria** have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.~~

~~**Phase I Oncology Liver Chemistry Increased Monitoring Criteria with continued therapy – Liver Monitoring Event**~~	
~~**Criteria**~~	~~**Actions**~~
~~ALT ≥3 x ULN **but** <5 x ULN **and** bilirubin <2 x ULN, **without** symptoms believed to be related to liver injury or~~	~~• Notify the GSK Medical Monitor **within 24 hrs** of learning of the abnormality to discuss subject safety~~ ~~• Subject can continue study treatment~~

hypersensitivity **and** who can be monitored weekly for 4 weeks	• Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3 x ULN and bilirubin <2 x ULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.
Subject with documented liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN ALT ≥3 x ULN and 1.5 x baseline value **but** ALT <5 x ULN and 2 x baseline value **and** bilirubin <2 x ULN, **without** symptoms believed to be related to liver injury, or hypersensitivity **and** who can be monitored weekly for 4 weeks	**For subjects with documented liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN** • If, after 4 weeks of monitoring, ALT <3 x ULN and <1.5 x baseline value, and bilirubin <2 x ULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline

References:

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Protein Adducts in Adults with Acetaminophen Overdose and Acute Liver Failure. *Drug Metab Dispos*. 2009;37(8):1779-1784.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. *J Clin Microbiol*. 2005;43(5):2363-2369.

Section 16.6 Appendix 6: Liver Safety Drug Restart/Rechallenge Guidelines

REVISED TEXT

1. Rechallenge Following Liver Stopping Events that are Possibly Related to Study Treatment (third bullet)

- subject currently exhibits severe liver injury defined by: alanine aminotransferase (ALT) ~~>~~≥3xULN, bilirubin ~~>~~≥2xULN (direct bilirubin >35% of total), or international normalization ratio (INR) >1.5

Section 16.7 Appendix 7: Genetic Research (new section; subsequent sections were renumbered)

NEW TEXT

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- **Response to medicine, including any treatment regimens under investigation in this study or any concomitant medicines;**
- **Cancer susceptibility, severity, and progression and related conditions**

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- **A 6-mL blood sample will be taken for deoxyribonucleic acid (DNA) extraction. A blood sample is collected at the baseline visit (Day 1 preferably for this study), after the subject has been randomized and provided informed consent for genetic research. If a subject initially declines to participate in genetic research and then changes their mind, a sample should be obtained at the earliest opportunity. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.**

The genetic sample is labelled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GlaxoSmithKline (GSK) may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the clinical study. Genetic informed consent must be obtained prior to any blood being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- **Continue to participate in the genetic research in which case the genetic DNA sample is retained**
- **Discontinue participation in the genetic research and destroy the genetic DNA sample**

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- **If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.**
- **Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.**

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the

investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

16.9.3. Protocol changes for Amendment 3 (24-Jun-2016) from Protocol Amendment 2 (26-Feb-2015)

Where the Amendment Applies

This amendment applies to all sites and countries.

Summary of Amendment Changes with Rationale

Amendment 3 incorporates changes to update the risk assessment section and to include additional requirements for monitoring of renal events following an INDSR report for Acute Renal Failure in a subject enrolled in this study.

In addition, it was clarified that subjects with disease progression defined by PSA progression alone or for the worsening of an isolated disease site that is not clinically significant are not required to discontinue treatment in the study. Separate definitions for disease progression as a study endpoint and disease progression mandated by the protocol to result in a subject being withdrawal from treatment is clarified.

Optional pharmacodynamics paired biopsies as well as clarifications around biomarker assessments were added to the Time and Events tables for the Dose Escalation and Dose Expansion Phases.

Additional language was added to clarify that the decision to terminate the Dose Expansion Phase will take into account all relevant factors, including but not solely based upon the statistical methodology and futility criterion.

Other minor clarifications and corrections of inadvertent errors were also added.

List of Specific Changes:

Throughout this section, added text has been bolded and deleted text had been shown with strikethrough. The remaining text has been shown to provide context for the changes.

Changes associated with renal assessments:

Section 1.4.1.1, Risk assessment for GSK2636771:

Renal: Degenerative changes were observed in the kidneys of rats and dogs at 100 mg/kg/day or 1000 mg/kg/day, including cellular and tubular changes, with chemistry and urinalysis findings. Grade 3, treatment-related hypophosphatemia and hypocalcaemia have been observed in the FTIH study P3B115717. **There have been 2 reports of acute kidney injury (grade 2 and 3) in subjects who received GSK2636771 in Study 200331. Since it is possible that GSK2636771 may contribute to acute kidney injury, renal events should be closely monitored**. Medical history will be collected and, physical examination and clinical laboratory tests will be measured frequently during therapy to monitor for potential toxicity. Guidelines **will be implemented** including dose modification and discontinuation (Section 7.3.1) for the management of renal insufficiency or renal-related events considered to be related to study treatment, ~~will be implemented~~. **It is recommended that patients be well hydrated and avoid the use of NSAIDs.**

Section 4.1.2, Inclusion Criterion 11:

Changes to requirements for adequate baseline organ function at time of Screening to include **serum phosphate within normal limits**, rather than ≤ Grade 1; and to require the use of the **CKD-EPI equation** rather than by the Cockcroft-Gault formula when estimating serum creatinine clearance.

Section 7.3.1, Management Guidelines for Renal Insufficiency:

Management guidelines for renal insufficiency or other renal events are to be followed when **serum creatinine ≥0.3 mg/dL (≥26.5 µmol/L)** rather than when serum creatinine ≥0.5 mg/dL (≥44.2 µmol/L), and are to include an assessment of **24-hour urine creatinine clearance, where feasible.**

In addition,

- If repeat serum creatinine fails to confirm increase, continue treatment with GSK2636771 at same dose level without interruption **and obtain blood sample for PK analysis , within 24-72 hrs after the last dose (refer to Section 8.7.3.1 for details on PK sample collection)**

Section 7.3.4 and Section 7.3.5, Management Guidelines for Diarrhea and Vomiting

A cross reference to Section 11.3 on hydration was added to this section on the management of diarrhea and the section on vomiting.

Section 10.1, Permitted Medications:

Concomitant medication and non-drug therapies was updated to note, **Use of NSAIDs should be avoided during the study.**

Section 11.3 Other Lifestyle Restrictions:

Lifestyle restrictions was updated to include the addition, **Subjects are to be instructed to avoid dehydration while participating in the study. Subjects who have inadequate oral intake or who have difficulty maintaining hydration should discontinue treatment with GSK2636771 until adequate oral intake can be maintained. If the subject must discontinue treatment for more than 14 days due to inadequate oral intake, the subject should be withdrawn from the study.**

Appendix 3:

Updated to remove the Cockcroft-Gault Formula and to add the web address for the CKD-EPI equation.

Change associated with clarification of the distinction between disease progression as and endpoint and as a criterion for the discontinuation of treatment

Section 5.2, Permanent Discontination of Study Treatment:

Study treatment(s) will be permanently discontinued for any of the following reasons:

- Disease progression **defined with regards to termination of study treatment as: Radiographic progression in soft tissue or bone by RECIST 1.1 for subjects with measurable disease, OR**
- **Bone progression on bone scan according to the criteria (Section 8.8.2.2), OR**
- **When it is determined in the opinion of the treating physician in collaboration with the subject that the subject is no longer clinically benefitting (NLCB) from treatment.**

NOTE: Subjects who are tolerating therapy and meet criteria for disease progression solely on the basis of rising PSA or for the worsening of an isolated disease site that is not clinically significant will NOT be required to discontinue treatment and can continue treatment until they are NLCB from treatment [Scher, 2016].

NOTE: Subjects must meet the PCWG2 guidelines for disease progression to avoid premature discontinuation of study treatment(s).

- ~~***Treatment Discontinuation due to PSA rise:*** Following PCWG2 guidelines, subjects should not be discontinued from study treatment(s) solely due to PSA rise during the first 12 weeks of treatment (Section 8.8.2.1).~~

- ~~***Treatment Discontinuation due to Bone Scan changes:*** Subjects should not be discontinued from study treatment(s) due to the occurrence of bone scan changes in the first 12 weeks that do not meet PCWG2 guidelines for progression (Section 8.8.2.2).~~

Section 5.3, Subject Completion:

A subject will be considered to have completed the study if the subject dies or **discontinues treatment due to disease progression** ~~otherwise progre~~sses during the study treatment or post-treatment follow-up period. All other subjects will be considered to have withdrawn from the study.

Section 8.1, Change in the column heading for Table 15 Time and Event Table for the Dose Escalation Phase and Table 16 Time and Event Table for the Dose Expansion Phase and addition of explanatory footnote 31:

Time of **Discontinuation of Treatment due to** Disease Progression[31]

31. Subjects are not required to discontinue treatment on the basis of PSA progression alone or for the worsening of an isolated disease site that is not clinically significant (see Section 5.2).

Section 8.8.1, Clinical Activity Endpoint:

The secondary endpoint to evaluate the clinical activity of oral GSK2636771 + enzalutamide **will be assessed using the disease progression endpoint (see Section 8.8.2.3) which differs from the disease progression criteria that lead to discontinuation of treatment (see Section 5.2**). ~~is the PSA and RECIST response rate as per PCWG2 guidelines.~~ CTC response will also be determined and reported as an exploratory endpoint.

Section 8.8.2.3, Disease Progression Endpoint:

The disease progression **endpoint** is defined by 1 or more of the following criteria:

- PSA progression according to the PCWG2 criteria (Section 8.8.2.1)
- Radiographic progression in soft tissue or bone by RECIST 1.1 for subjects with measurable disease
- Bone progression on bone scan according to the PCWG2 criteria (Section 8.8.2.2).

Subjects are not required to discontinue treatment on the basis of meeting PSA progression alone or for the worsening of an isolated disease site that is not clinically significant (see Section 5.2)

References:

Citation for the Prostate Cancer Clinical Trials Working Group 3 [Scher, 2016] was added.

Other minor changes:

To conform to changes added in Section 5.2 regarding when treatment is to be discontinued

- A cross reference to Section 5.2 was added to Section 3.2.3 and Section 3.3, and
- Clarifications were added to Section 3.5 and Section 8.1 (Time and Events Table 15 and Table 16).

Changes associated with the addition of optional paired biopsies for pharmacodynamics analysis as well as clarifications around biomarkers, including assessments added to the Time and Events tables for the Dose Escalation and Dose Expansion Phases.

Section 2.2 Objective and Endpoints:

Addition of the following study objective and endpoint:

- To determine pharmacodynamic effects of drug treatment
- RNA/protein analysis of pre/post treatment tumor biopsies

Section 3.0, Investigational Plan:

Biomarker Assessments: Planned biomarker assessments include: 1) Identify potential predictive biomarkers (protein, DNA, ribonucleic acid [RNA] based) in archived tumor tissue/pre-treatment biopsies; 2) enumeration of CTCs in circulation and evaluation of **genetic** alterations **or expression of** ~~in~~AR,~~or~~PTEN **or other** genes ~~(or other genomic markers)~~ in isolated CTCs; 3) Assessment of ~~gene mutations in~~ circulating~~free~~ DNA/**RNA** ~~(cfDNA)~~ and other soluble markers in plasma to better understand clonal evolution and other predictive circulating biomarkers; and 4) understand the mechanism of resistance in tumor tissues biopsies (optional) at time of progression **5) assess pharmacodynamic effects by collecting pre/post treatment tumor biopsies**

Section 3.4 Dose Escalation Plan

If the combination doses in Cohort 1 are not tolerable, lower doses ~~as defined in the de-escalation cohort (Cohort -1)~~ will be evaluated. If the de-escalation cohort (Cohort -1) is not tolerable, ~~further dose escalation using a continuous daily dosing schedule for both compounds simultaneously will be terminated.~~additional dose levels of GSK2636771 or alternative dosing schedules may be explored based upon ongoing assessment of safety,

PD and PK. Dose modification decisions will be made utilizing all available data at the end of each DLT reporting period (the first 28 days of combination treatment).

Section 8.1, Time and Events Tables:

Additional unplanned blood, plasma and/or optional tumor samples may be requested with patient consent and investigator agreement as needed to better characterize safety and response(s) in subjects.

Table 15 Time and Events Table for the Dose Escalation Phase and Table 16 Time and Events Table for the Dose Expansion Phase:

cfDNA/RNA/Soluble Marker updated to include plasma samples collected pre-dose at **Weeks 1, 8, 16, 24, and 32**.

Footnote 24:

24. Tumor Biopsies for PD and progression: **These biopsies are optional and may be undertaken in select cases upon agreement with the investigator and when consent is provided by the subject. For pharmacodynamic biomarker analyses, fresh tissue biopsies would be collected between Day 12 of the Enzalutamide Run-in Period and Week 1/Day 1, prior to any treatment with GSK2636771, and 2-4 hours post dose between Days 8 and 15 of the Combination Treatment Period (post-treatment). For subjects who consent to the optional progression biopsy, a fresh tumor biopsy should be completed if the subject initially responded to combination treatment and then progressed.**

LDH assessments added, along with a footnote 32

32. When collected as part of the routine standard of care for a subject, LDH will be reported.

Section 8.9.2, Tumor Sample Biopsies:

If consent is provided by the subject, **optional fresh tumor biopsies may be collected prior to combination treatment and 2 to 4 hours post dose on day 8 or 15 of combination treatment to understand target engagement and pharmacodyamic effects. It is preferable to repeat biopsy the same lesion to get a clearer picture of pre and post treatment effects.** For subjects who initially responded to combination therapy and then progressed, an optional progression tumor biopsy is requested in order to better understand the mechanism of resistance. It is preferable to obtain this biopsy from a new lesion or a lesion which had previously responded and then progressed. Biopsy samples from other lesions will be accepted as well. Both soft tissue and bone biopsies will be accepted.

Section 8.9.4, Circulating Cell Free Tumor DNA, RNA and Soluble Markers:

Furthermore, cfDNA in cancer subjects can harbor many genetic alterations (mutations, **copy number changes** ~~microsatellite alterations~~, aberrant methylation), which are generally consistent with the tumor **of origin**.

Section 8.11, Explorator PK and PD Analysis:

Evaluation of **pre and post treatment tumor tissue may also be explored to determine pharmacodynamic effects** and the mechanism of resistance to combination therapy in subjects who have progressed after initially responding to the combination therapy.

Section 13.3.4.5, Translational Research Analyses:

Plasma collection at baseline, post-treatment and at time of disease progression will be used to analyze cfDNA, RNA and other soluble markers to understand clonal evolution, **monitor response and explore** ~~and other~~ predictive ~~circulating~~ biomarkers. Archival ~~tissue/pre-dose~~ **or fresh** biopy tissue may be utilized to identify potential predictive biomarkers (protein, DNA and RNA based markers). Optional **PD** and progression biopsies for subjects who have progressed from initially responding to the combination therapy may also be requested to understand **pharmacodynamic effects and** mechanism(s) of resistance.

Changes associated with the futility criterion for the Dose Expansion Phase

Section 3.6.1, Evaluation of Futility

~~All available data will be considered in making enrollment decisions.~~

The decision to terminate the Dose Expansion Phase will not depend solely on the results of the statistical methodology, but will take all factors into account. These factors include the representation of predictive biomarkers, such as Androgen receptors, in the subjects treated at the time of interim analysis; and the totality of the safety, tolerability, PK, and PD data. Additional subjects targeting a specific biomarker profile may be enrolled in the cohort at the discretion of the team even if the predictive probability suggests a low likelihood of clinical activity in this cohort

Section 13.2.2, Dose Expansion Phase

However, the decision to terminate the Dose Expansion Phase will not depend solely on the results of the statistical methodology, but will take all factors into account. Additional subjects in a cohort may be enrolled even if the predictive probability suggests a low likelihood of activity in the Expansion Cohort (see Section 3.6.1).

Other changes to provide additional clarifications or to correct inadvertent errors in previous versions of the protocol:

Section 1.2.1, Introduction:

Updated status of study P3B115717 to note the study is completed and enrolled 65 subjects.

Section 3.0 Cohort Expansion, 4th paragraph

In the Dose Expansion Phase, subjects will be assigned to receive GSK2636771 at **doses identified at or below** the MTD ~~or RP2D determined~~ in the Dose Escalation Phase while continuing treatment with enzalutamide to evaluate the long-term safety of the combination as well as the 12-week non-PD rate.

Section 3.2.4, Post Treatment Follow up

Subjects who discontinue the Extended Follow-Up Visits prior to disease progression, **for reasons other than** death, **loss to follow-up,** or withdrawal of consent should have a Post-Extended Follow-Up/EOS Visit performed.

Section 3.4.1, Cohort Expansion:

Subjects may be enrolled at previously completed dose levels for the purpose of obtaining additional PK and/or PD data

Section 3.5 Dose Expansion Phase

Enrollment in the Dose Expansion Phase of the study may begin once the MTD and RP2D have been determined in the Dose Escalation Phase. Up to 20 additional subjects may be enrolled to better characterize the safety profile, PK, and clinical activity of the recommended **doses** of the combination of GSK2636771 + enzalutamide for future studies. **One or more combination doses may be explored in the Dose Expansion Phase based the MTD and RP2D identified in the Dose Escalation Phase of the study.**

Section 4.1.3, Exclusion Criteria 1:

Added clarification that treatment with abiraterone during the study is exclusionary to enrollment.

Section 7.3.3 Management Guidelines for Rash:

An error in previous versions of the protocol was corrected in the rash management guidelines to indicate that treatment can be restarted following rash events when rash returns to **≤ Grade 1**, rather than < Grade 1.

A note was also added to include PK samples for Grade 3 and Grade 4 dose limiting toxicity rash events.

Section 8.1, Time and Events Tables:

Table 15 Time and Events Table for the Dose Escalation Phase and Table 16 Time and Events Table for the Dose Expansion Phase:

CTC- **Janssen**

Section 8.6.6, Table 17, Laboratory Assessments:

Added **Hematocrit** to the list of laboratory assessments.

Section 8.8.2.1 and Section 8.8.2.2:

Clarification was added to note that PSA response and response in bone is to be assessed following 12 weeks of **combination** treatment with enzalutamide plus GSK2636771.

16.9.4. Protocol changes for Amendment 4 (27-Jan-2017) from Protocol Amendment 3 (24-Jun-2016)

Where the Amendment Applies

This amendment applies to all sites and countries.

Summary of Amendment Changes with Rationale

Amendment 4 was completed to include additional requirements for monitoring of events related to calcium results, including revisions to the Table & Events to clarify additional laboratory testing requirements; clarification of secondary clinical activity endpoints and update to associated statistical section(s); revision of clinical activity population allowing the combination of dose escalation and dose expansion populations; revision of dose escalation and dose expansion wording to allow multiple dose levels in dose expansion to establish RP2D after dose expansion phase; adjustment to Week 12 visit window and clarification for Week 12 assessment timing; revision to reflect current indication for enzalutamide throughout; clarification of study populations; clarification of bone progression definition.

Other minor clarifications and corrections of inadvertent errors were also added.

List of Specific Changes:

Throughout this section, added text has been bolded and deleted text had been shown with strikethrough. The remaining text has been added to provide context for changes.

Synopsis – Study Rationale:

Rationale for Change:

Revision to reflect currently approved indication for enzalutamide.

Previous text:

Therapeutic approaches that simultaneously inhibit both the androgen receptor (AR) pathway and the PI3K pathway may be more effective than inhibition of either pathway alone in mCRPC. Enzalutamide is an AR inhibitor indicated for the treatment of patients with mCRPC who have previously received docetaxel. The proposed Phase I study will evaluate the safety and tolerability, pharmacokinetics (PK), and clinical activity to determine the recommended Phase II dose (RP2D) and regimen of GSK2636771 in combination with enzalutamide given orally in adult male subjects with mCRPC.

Revised text:

Therapeutic approaches that simultaneously inhibit both the androgen receptor (AR) pathway and the PI3K pathway may be more effective than inhibition of either pathway alone in mCRPC. Enzalutamide is an AR inhibitor indicated for the treatment of patients with mCRPC ~~who have previously received docetaxel~~. The proposed Phase I study will evaluate the safety and tolerability, pharmacokinetics (PK), and clinical activity to determine the recommended Phase II dose (RP2D) and regimen of GSK2636771 in combination with enzalutamide given orally in adult male subjects with mCRPC.

Synopsis – Secondary Hypothesis:

Rationale for Change:

Update of study population in hypothesis wording

Previous text:

Secondary Hypothesis: The addition of a targeted PI3K pathway inhibitor (GSK2636771) to enzalutamide can limit mCPRC progression in a clinically meaningful way for at least 12 weeks. The null hypothesis is that the 12-week non-progressive disease (PD) rate is not attractive (≤5%). The alternative hypothesis is that the rate is clinically meaningful and, therefore, the compound warrants further development (≥30%). This hypothesis will be tested for Part 2 of the study only.

Revised text:

Secondary Hypothesis: The addition of a targeted PI3K pathway inhibitor (GSK2636771) to enzalutamide can limit mCPRC progression in a clinically meaningful way for at least 12 weeks. The null hypothesis is that the 12-week non-progressive disease (PD) rate is not attractive (≤5%). The alternative hypothesis is that the rate is clinically meaningful and, therefore, the compound warrants further development (≥30%). This hypothesis will be tested for Part 2 of the study, ~~only~~ **combining eligible subjects from Part 1.**

Synopsis – Primary Objectives:

Rationale for Change:

Changes to the abbreviations used in this section, by writing out all abbreviations s first instance in the synopsis. These included writing out AE (Adverse Events), SAEs (Serious

Adverse Events), DLTs (Dose Limiting Toxicities, ECGs (Electrocardiograms) and BP (Blood Pressure). Adjustment to efficacy endpoint wording.

Previous text:

- Non-PD rate for 12 weeks according to 2PCWG2 criteria (either by RECIST 1.1, PSA progression, and/or progression in bone).

Revised text:

- Non-PD rate for 12 weeks according to ~~2~~PCWG2 criteria (either by R**esponse** E**valuation** C**riteria** I**n** S**olid Tumors [**RECIST**]** 1.1, or progression in bone **or** P**rostate** S**pecific** A**ntigen [**PSA**]** progression **with accompanying progression by RECIST 1.1 or bone scan when baseline radiological or bone disease present or PSA progression if no other baseline disease**).

Synopsis – Secondary Objectives:

Rationale for Change:

Deletion of wording associated with how additional clinical activity was to be measured with less defined endpoints. Addition new secondary objective and endpoints.

Previous text:

• To evaluate the clinical activity of oral GSK2636771 + enzalutamide in the treatment of mCRPC (PTEN deficient)	• PSA as defined in PCWG2 guidelines and RECIST 1.1 response.

Revised text:

• To evaluate the clinical activity of oral GSK2636771 + enzalutamide in the treatment of mCRPC (PTEN deficient)	• **PSA50 response rate defined as the percent of subjects achieving PSA50 at 12 weeks or thereafter (PSA50 is ≥50% decrease in PSA from baseline)** • **Objective Response Rate (ORR) defined as complete response (CR) rate plus partial response (PR) rate per RECIST 1.1** • **Time to PSA progression according to PCWG2 criteria** • **Time to radiological progression according to PCWG2 criteria (either by RECIST 1.1, and/or progression in bone)** • **Radiological progression free survival (rPFS) per RECIST1.1 and/or bone scans** • ~~PSA as defined in PCWG2 guidelines and RECIST 1.1 response.~~

Synopsis – Dose escalation Cohort Expansion:

Rationale for Change:

Due to possibility of multiple doses being explored in dose expansion, updated wording to clarify dose escalation population and how maximum tolerated dose will be defined.

Previous text:

Cohort Expansion: Selected dose levels may enroll up to 12 additional subjects to ensure a sufficient number of subjects enrolled to assess PK and/or safety. The MTD will be the recommended dose combination for future Phase II studies unless there is a lower dose of GSK2636771 that provides adequate PK exposure and biologic activity with superior tolerability.

Revised text:

Cohort Expansion: Selected dose levels may enroll up to 12 additional subjects to ensure a sufficient number of subjects enrolled to assess PK and/or safety. The MTD **may** ~~will~~ be the recommended dose combination for future Phase II studies unless there is a lower dose of GSK2636771 that provides adequate PK exposure and biologic activity with superior tolerability. **The final decision will be based on the totality of data.**

Synopsis – Dose Expansion Phase:

Rationale for Change:

Clarification that multiple doses may be explored in the dose expansion phase.

Previous text:

This phase of the study will evaluate the long term safety of the combination treatment as well as the 12-week non-progressive disease (PD) rate of the combination treatment in subjects with mCPRC. Approximately 20 subjects will be enrolled with each subject assigned to receive GSK2636771 in combination with enzalutamide.

Revised text:

This phase of the study will evaluate the long term safety of the combination treatment as well as the 12-week non-progressive disease (PD) rate of the combination treatment in subjects with mCPRC. ~~Approximately 20 subjects will be enrolled with each subject assigned to receive GSK2636771 in combination with enzalutamide.~~**To confirm dose(s) identified during dose escalation, multiple dose levels of GSK2636771 in combination with enzalutamide may be examined during dose expansion, with each dose level cohort enrolling up to 20 subjects. Using the totality of safety, PK and clinical activity data, the RP2D will be confirmed from the dose level(s) which are examined in the dose expansion phase.**

Synopsis – Number of Subjects Study Design:

Rationale for Change:

Updated of the potential number of subjects due to possibility of multiple dose expansion cohorts and clarification of wording due to combination of dose escalation and expansion populations.

Previous text:

A total of approximately 44 subjects will be enrolled in this study.

In the Dose Escalation Phase, the number of dose levels and the level at which the MTD is reached cannot be determined in advance. An adequate number of subjects will be enrolled to establish the RP2D. It is estimated that approximately 24 subjects will be enrolled to allow assessment of safety and preliminary efficacy in PTEN-deficient mCRPC with disease progression on enzalutamide.

In the Dose Expansion Phase, it is estimated that approximately 20 subjects will be enrolled, with evaluation for futility after the first 10 subjects have completed 12 weeks of treatment. The sample size planned for the Dose Expansion Phase is not driven by statistical considerations as the cohort is meant to further understand the safety implications of enrolling subjects to combination therapy for an extended period of time.

Revised text:

A total of approximately 44 **to 64** subjects will be enrolled in this study.

In the Dose Escalation Phase, the number of dose levels and the level at which the MTD is reached cannot be determined in advance. An adequate number of subjects will be enrolled to establish the ~~RP2D~~ **MTD**. It is estimated that approximately 24 subjects will be enrolled to allow assessment of safety and preliminary efficacy in PTEN-deficient mCRPC with disease progression on enzalutamide.

In the Dose Expansion Phase, it is estimated that approximately 20 subjects will be enrolled, with evaluation for futility after the first 10 subjects have completed 12 weeks of treatment. **This analysis may occur using the combination of the dose escalation and dose expansion population. If multiple dose levels of GSK2636771 are examined during dose expansion to establish the RP2D, each dose level cohort will enrol approximately 20 subjects, increasing the overall number of subjects targeted for enrolment in this study.** The sample size planned for the Dose Expansion Phase is not driven by statistical considerations as the cohort is meant to further understand the safety implications of enrolling subjects to combination therapy for an extended period of time.

Synopsis – Inclusion Criteria 11:

Rationale for Change:

Due to updated changes for calcium and bone markers adjusted the Other section of the tests in this criteria and updated footnote, by adding footnote 6.

Previous text:

Other	
Serum Phosphate[6]	WNL
Serum Calcium (corrected)	WNL

6.Per CTCAE v4.0, Grade 1 hypophosphatemia is <LLN – 2.5 mg/dL (<LLN - 0.8 mmol/L

Revised text:

Other	
Serum Phosphate[6]	WNL
Serum Calcium[6] (corrected)	
Ionized Calcium[6]	WNL
Vitamin D[6]: 25-OH D and	**WNL**
1,25-OH2 D	**WNL**

6. ~~Per CTCAE v4.0, Grade 1 hypophosphatemia is <LLN – 2.5 mg/dL (<LLN - 0.8 mmol/~~Vitamin D supplementation may be added to achieve values WNL. Calcium supplements should be added for subjects with calcium values near the lower normal limit.

Synopsis – Safety Assessments:

Rationale for change:

Clarification of labs required for study based on emerging safety data.

Previous text:

Clinical chemistry: blood urea nitrogen, creatinine, glucose (fasting), sodium, potassium, chloride, carbon dioxide, calcium, aspartate aminotransferase (AST), ALT, alkaline phosphatase, total protein, albumin, uric acid and total/direct bilirubin, phosphorus, and magnesium.

Revised text:

Clinical chemistry: blood urea nitrogen, creatinine, glucose (fasting), sodium, potassium, chloride, carbon dioxide, calcium **(serum and ionized), vitamin D**, aspartate aminotransferase (AST), ALT, alkaline phosphatase, total protein, albumin, uric acid and total/direct bilirubin, phosphorus, and magnesium.

Synopsis – Statistical Methods:

Rationale for change:

Revision of hypotheses to allow analyses on combined dose escalation and expansion cohorts.

Previous text:

Hypothesis: No formal statistical hypotheses will be tested in the Dose Escalation Phase. All analyses will be descriptive and exploratory for this phase.

A targeted PI3K pathway inhibitor (GSK2636771) added to enzalutamide will be tested to see if mCPRC progression can be limited in a clinically meaningful way for at least 12 weeks. The null

hypothesis is that the 12-week non-PD rate is not attractive (≤5%). The alternative hypothesis is that the rate is clinically meaningful and therefore, the compound warrants further development (≥30%).

For the Dose Expansion Phase, utilizing a null and alternative hypothesis of 5% and 30% respectively, a maximum of 20 subjects will be enrolled, with a minimum enrollment of 10 subjects. With an actual type I error rate (α) of 0.065 and 94.2% power, the design has stopping criteria defined for futility.

Number of Subjects Enrolled	≤ This Number of Responses[1] to Stop Early for Futility
10	0
11	0
12	0
13	0
14	0
15	0
16	1
17	1
18	1
19	1
20	2

Abbreviation: PCWG2, Prostate Cancer Working Group 2

1. Response for the purpose of futility is defined as lack of disease progression at 12 weeks according to PCWG2 criteria.

Revised text:

Hypothesis: No formal statistical hypotheses will be tested in the Dose Escalation Phase. All analyses will be descriptive and exploratory for this phase.

~~A targeted PI3K pathway inhibitor (GSK2636771) added to enzalutamide will be tested to see if mCPRC progression can be limited in a clinically meaningful way for at least 12 weeks. The null hypothesis is that the 12-week non-PD rate is not attractive (≤5%). The alternative hypothesis is that the rate is clinically meaningful and therefore, the compound warrants further development (≥30%).~~

For the Dose Expansion Phase, **clinical activity will be evaluated per dose level if more than one dose is examined. A targeted PI3K pathway inhibitor (GSK2636771) added to enzalutamide will be tested to see if mCPRC progression can be limited in a clinically meaningful way for at least 12 weeks. The null hypothesis is that the 12-week non-PD rate is not attractive (≤5%). The alternative hypothesis is that the rate is clinically meaningful and therefore, the compound warrants further development (≥30%). All evaluable subjects treated during dose escalation and in the dose expansion Phase will be included in analyses.** ~~utilizing a null and alternative hypothesis of 5% and 30% respectively, a~~ **A** maximum of 20 subjects **per dose level** ~~will~~ **may** be enrolled, with a minimum enrollment of 10 subjects. With an actual type I error rate (α) of 0.065 and 94.2% power, the design has stopping criteria defined for futility **as follows**.

Number of Subjects Enrolled	≤ This Number of Responses[1] to Stop Early for Futility
10	0
11	0
12	0
13	0
14	0
15	0
16	1
17	1
18	1
19	1
20	2

Abbreviation: PCWG2, Prostate Cancer Working Group 2

1. Response for the purpose of futility is defined as lack of disease progression at 12 weeks according to PCWG2 criteria. **PSA progression in subjects with baseline radiological or bone disease will require RECIST or bone progression in addition to PSA progression to be determined a disease progressor.**

Synopsis – Statistical Methods Study Populations:

Rationale for change:

Revised and added population to clarify between safety and clinical activity populations and to define the evaluable population for endpoint analyses.

Previous text:

The **All Treated Population** is defined as all subjects who receive at least one dose of GSK2636771. Safety, clinical activity, and evaluation of non-PD rate in the Dose Expansion Phase will be evaluated based on this analysis population.

The **PK Population** will consist of all subjects from the All Treated Population for whom at least one PK sample is obtained and analyzed.

The **All Screened Population** is defined as all subjects for whom pre-screening consent is obtained.

Efficacy Analyses: The All Treated Population will be used for the analysis of efficacy data, and summarized separately for each part of the study. Response data per 2PCWG2 and RECIST 1.1 guidelines will be reported. Further details about efficacy analyses will be outlined in detail in the RAP.

Safety Analyses: The All Treated Population will be used for the analysis of safety data. All serially collected safety endpoints (e.g., laboratory tests, vital signs, ECGs) will be summarized according to the scheduled, nominal visit at which they were collected and across all on-treatment time points using a “worst-case” analysis.

Revised text:

The All Treated **Safety** Population is defined as all subjects who receive at least one dose of GSK2636771 **or Enzalutamide**. Safety, clinical activity, and evaluation of non PD rate in the Dose Expansion Phase will be evaluated based on this analysis population.

The All Treated Clinical Activity Population is defined as all subjects who received at least one dose of GSK2636771. Clinical activity and evaluation of non-PD rate will be based on this analysis population. This will include subjects from both dose escalation and dose expansion.

The All Evaluable Population is defined as all subjects from All Treated Clinical Activity Population who have at least one post-dose disease assessment and have been exposed to study drug for at least 12 weeks or have progressed or have died or have withdrawn from the study for any reason. Dose Expansion futility analyses will be based on this population.

The PK Population will consist of all subjects from the All Treated Population for whom at least one PK sample is obtained and analyzed.

~~The **All Screened Population** is defined as all subjects for whom pre-screening consent is obtained.~~

Efficacy Analyses: The All Treated **Clinical Activity** Population will be used for the analysis of efficacy data, and **will be** summarized separately ~~for each part of the study~~ **per dose level**. Response data per ~~2~~PCWG2 and RECIST 1.1 guidelines will be reported. Further details about efficacy analyses will be outlined in detail in the RAP.

Safety Analyses: The All Treated **Safety** Population will be used for the analysis of safety data. All serially collected safety endpoints (e.g., laboratory tests, vital signs, ECGs) will be summarized according to the scheduled, nominal visit at which they were collected and across all on-treatment time points using a "worst-case" analysis.

Section 1.3 – Enzalutamide (Xtandi):

Rationale for change:

Updated section to reflect currently approved indication for enzalutamide. Updated citation in the body of the text and added the citation in the Reference section.

Previous text:

Enzalutamide (Xtandi) is an orally bioavailable, AR signalling inhibitor approved in the United States (US) and the European Union for the treatment of patients with mCRPC who have previously received treatment with docetaxel [Xtandi, 2013]. Enzalutamide acts on several steps in the AR signaling pathway, including competitive inhibition of androgen binding to ARs and inhibition of AR nuclear translocation and its interaction with deoxyribonucleic acid (DNA). A major metabolite, N-desmethyl enzalutamide, exhibited similar *in vitro* activity to enzalutamide.

Refer to to the approved US Food and Drug Administration (FDA) prescribing information [Xtandi, 2013] or the Xtandi Prescribing Information for the area where it is approved for further details.].

Revised text:

Enzalutamide (Xtandi) is an orally bioavailable, AR signalling inhibitor approved in the United States (US) and the European Union for the treatment of patients with mCRPC ~~who have previously received treatment with docetaxel~~ [Xtandi, 201~~3~~**6**]. Enzalutamide acts on several steps in the AR signaling pathway, including competitive inhibition of androgen binding to ARs and inhibition of AR nuclear translocation and its interaction with deoxyribonucleic acid (DNA). A major metabolite, N-desmethyl enzalutamide, exhibited similar *in vitro* activity to enzalutamide.

Refer to to the approved US Food and Drug Administration (FDA) prescribing information [Xtandi, 201~~3~~**6**] or the Xtandi Prescribing Information for the area where it is approved for further details.].

Section 1.3.1 – Clinical Safety, Pharmacokinetic Data, and Clinical Activity of Enzalutamide:

Rationale for change:

Updated citation in the body of the text and added the citation in the Reference section.

Previous text:

Clinical Response. In a randomized, double-blinded, Phase III clinical trial comparing enzalutamide with placebo in subjects with mCRPC who had progressed following docetaxel-based chemotherapy, enzalutamide prolonged overall survival by 5 months (median survival of 18.4 months with enzalutamide [n=800] compared to 13.6 months with placebo [N=399]) which is statistically and clinically significant [Xtandi, 2013]. Enzalutamide is approved in the US, Canada, the European Union and others (refer to Xtandi Prescribing Information in the relevant jurisdiction). Recently, enzalutamide has also been shown to improve survival (32.4 months vs. 30.2 months) in chemotherapy-naïve subjects with advanced prostate cancer in a separate Phase III, randomized, placebo-controlled study [Beer, 2014].

Refer to the approved US FDA prescribing information [Xtandi, 2013] or the Xtandi Prescribing Information for the area where it is approved for further details.

Revised text:

Clinical Response. In a randomized, double-blinded, Phase III clinical trial comparing enzalutamide with placebo in subjects with mCRPC who had progressed following docetaxel-based chemotherapy, enzalutamide prolonged overall survival by 5 months (median survival of 18.4 months with enzalutamide [n=800] compared to 13.6 months with placebo [N=399]) which is statistically and clinically significant [Xtandi, 201~~3~~**6**]. Enzalutamide is approved in the US, Canada, the European Union and others (refer to

Xtandi Prescribing Information in the relevant jurisdiction). Recently, enzalutamide has also been shown to improve survival (32.4 months vs. 30.2 months) in chemotherapy-naïve subjects with advanced prostate cancer in a separate Phase III, randomized, placebo-controlled study [Beer, 2014].

Refer to the approved US FDA prescribing information [Xtandi, 201~~3~~**6**] or the Xtandi Prescribing Information for the area where it is approved for further details.

Section 1.4 – Summary of Risk Management:

Rationale for change:

Updated citation in the body of the text and added the citation in the Reference section.

Previous text:

Refer to the GSK2636771 IB [GlaxoSmithKline Document Number 2011N117133_01] for detailed information concerning the biology, pharmacology, PK and safety. Refer to approved US FDA prescribing information [Xtandi, 2013] or the Xtandi Prescribing Information for the area where it is approved for additional information.

Revised text:

Refer to the GSK2636771 IB [GlaxoSmithKline Document Number 2011N117133_01] for detailed information concerning the biology, pharmacology, PK and safety. Refer to approved US FDA prescribing information [Xtandi, 201~~3~~**6**] or the Xtandi Prescribing Information for the area where it is approved for additional information.

Section 1.4.1.1 Risk Assessment - GSK2636771:

Rationale for change:

Section was updated to reflect updated information and to reflect changes in the core information sheet.

Previous text:

Renal: Degenerative changes were observed in the kidneys of rats and dogs at 100 mg/kg/day or 1000 mg/kg/day, including cellular and tubular changes, with chemistry and urinalysis findings. Grade 3, treatment-related hypophosphatemia and hypocalcaemia have been observed in the FTIH study P3B115717. There have been 2 reports of acute kidney injury (grade 2 and 3) in subjects who received GSK2636771 in Study 200331. Since it is possible that GSK2636771 may contribute to acute kidney injury, renal events should be closely monitored. Medical history will be collected and, physical examination and clinical laboratory tests will be measured frequently during therapy to monitor for potential toxicity. Guidelines will be implemented including dose modification and discontinuation (Section 7.3.1) for the management of renal insufficiency or renal-related events considered to be related to study treatment. It is recommended that patients be well hydrated and avoid the use of NSAIDs.

Revised text:

Renal **and electrolytes**: Degenerative changes were observed in the kidneys of rats and dogs at 100 mg/kg/day or 1000 mg/kg/day, including cellular and tubular changes, with chemistry and urinalysis findings. **There have been serious, treatment-related reports of acute kidney injury, hypophosphatemia and hypocalcaemia in GSK2636771 clinical trials. Renal events should be closely monitored. It is recommended that patients be well-hydrated and avoid the use of NSAIDs. Calcium and Vitamin D levels will be monitored. Consider supplements in those with calcium levels at or near the lower normal limit and those with low Vitamin D levels.** ~~Grade 3, treatment-related hypophosphatemia and hypocalcaemia have been observed in the FTIH study P3B115717. There have been 2 reports of acute kidney injury (grade 2 and 3) in subjects who received GSK2636771 in Study 200331. Since it is possible that GSK2636771 may contribute to acute kidney injury, renal events should be closely monitored.~~ Medical history will be collected and, physical examination and clinical laboratory tests will be measured frequently during therapy to monitor for potential toxicity. Guidelines will be implemented including dose modification and discontinuation (Section 7.3.1) for the management of renal insufficiency**,** ~~or~~ renal-related events **or electrolyte abnormalities** considered to be related to study treatment. ~~It is recommended that patients be well hydrated and avoid the use of NSAIDs.~~

Section 1.5.1 – Rationale for Study

Rationale for change:

Updated citation in the body of the text and added the citation in the Reference section.

Previous text:

Despite recent advances in the treatment of advanced prostate cancer, relapses are inevitable and mCRPC carries considerable morbidity along with shortened survival. Previous studies have indicated the importance of the PI3K pathway in prostate cancer. Therapeutic approaches that simultaneously inhibit both the AR and PI3K pathways may be more effective than inhibition of either pathway alone in mCRPC. Enzalutamide is an AR inhibitor indicated for the treatment of patients with mCRPC who have previously received docetaxel. This study is designed to investigate whether the PI3K pathway inhibitor can be co-administered safely with enzalutamide, thus allowing further investigation of their ability to reverse resistance to this AR inhibitor. Future studies may also assess whether the combination can delay the onset of resistance in enzalutamide-naïve CRPC or increase the response rate to enzalutamide.

Revised text:

Despite recent advances in the treatment of advanced prostate cancer, relapses are inevitable and mCRPC carries considerable morbidity along with shortened survival. Previous studies have indicated the importance of the PI3K pathway in prostate cancer. Therapeutic approaches that simultaneously inhibit both the AR and PI3K pathways may be more effective than inhibition of either pathway alone in mCRPC. Enzalutamide is an AR inhibitor indicated for the treatment of patients with mCRPC ~~who have previously~~

~~received docetaxel~~. This study is designed to investigate whether the PI3K pathway inhibitor can be co-administered safely with enzalutamide, thus allowing further investigation of their ability to reverse resistance to this AR inhibitor. Future studies may also assess whether the combination can delay the onset of resistance in enzalutamide-naïve CRPC or increase the response rate to enzalutamide.

Section 2.1 – Hypothesis; Secondary Hypothesis:

Rationale for Change:

Update of study population in hypothesis wording

Previous text:

Secondary Hypothesis: The addition of a targeted PI3K pathway inhibitor (GSK2636771) to enzalutamide can limit mCPRC progression in a clinically meaningful way for at least 12 weeks. The null hypothesis is that the 12-week non PD rate is not attractive (≤5%). The alternative hypothesis is that the rate is clinically meaningful and, therefore, the compound warrants further development (≥30%). This hypothesis will be tested for Part 2 of the study only.

Revised text:

Secondary Hypothesis: The addition of a targeted PI3K pathway inhibitor (GSK2636771) to enzalutamide can limit mCPRC progression in a clinically meaningful way for at least 12 weeks. The null hypothesis is that the 12-week non PD rate is not attractive (≤5%). The alternative hypothesis is that the rate is clinically meaningful and, therefore, the compound warrants further development (≥30%). This hypothesis will be tested ~~for Part 2 of the study only~~ **using a combination of data provided in both the dose escalation and dose expansion phases.**

Section 2.2 Objectives and Endpoints – Primary Objectives:

Rationale for Change:

Adjustment to efficacy endpoint wording.

Previous text:

- Non-PD rate for 12 weeks according to PCWG2 criteria (either by RECIST 1.1, PSA progression, and/or progression in bone).

Revised text:

- Non-PD rate for 12 weeks according to PCWG2 criteria (either by RECIST 1.1, or progression in bone **or** PSA progression **with accompanying progression by RECIST 1.1 or bone scan when baseline radiological or bone disease present or PSA progression if no other baseline disease**).

Section 2.2 Objectives and Endpoints – Secondary Objectives:

Rationale for Change:

Deletion of wording associated with how additional clinical activity was to be measured with less defined endpoints. Addition new secondary objective and endpoints.

Previous text:

• To evaluate the clinical activity of oral GSK2636771 + enzalutamide in the treatment of mCRPC (PTEN deficient)	• PSA as defined in PCWG2 guidelines and RECIST 1.1 response.

Revised text:

• To evaluate the clinical activity of oral GSK2636771 + enzalutamide in the treatment of mCRPC (PTEN deficient)	• **PSA50 response rate defined as the percent of subjects achieving PSA50 at 12 weeks or thereafter (PSA50 is ≥50% decrease in PSA from baseline)** • **Objective Response Rate (ORR) defined as complete response (CR) rate plus partial response (PR) rate per RECIST 1.1** • **Time to PSA progression according to PCWG2 criteria** • **Time to radiological progression according to PCWG2 criteria (either by RECIST 1.1, and/or progression in bone)** • **Radiological progression free survival (rPFS) per RECIST1.1 and/or bone scans** • ~~PSA as defined in PCWG2 guidelines and RECIST 1.1 response.~~

Section 3 – Investigation Plan:

Rationale for Change:

Due to possibility of multiple doses being explored in dose expansion, updated wording to clarify dose escalation population and how maximum tolerated dose will be defined.

Previous text:

In the Dose Escalation Phase, subjects will be enrolled into dose-finding cohorts to evaluate the safety and PK to guide the selection of the RP2D of GSK2636771. Dosing decisions will be based on all available data at the end of each DLT reporting period (the first 28 days of combination treatment). Decisions for dose determination for subsequent

cohorts will be documented and maintained by each site and in the GSK Trial Master Files (TMF).

In the Dose Expansion Phase, subjects will be assigned to receive GSK2636771 at doses identified at or below the MTD in the Dose Escalation Phase while continuing treatment with enzalutamide to evaluate the long-term safety of the combination as well as the 12-week non-PD rate.

Clinical Response Assessments: The determination of clinical response, including disease progression, will be assessed by the PCWG2 criteria (see Section 8.8.2). The assessment of the 12 week non-PD-rate in the Dose Expansion Phase will also be determined by 2PCWG2 criteria (either by RECIST 1.1, PSA progression, and/or progression in bone).

Revised text:

In the Dose Escalation Phase, subjects will be enrolled into dose-finding cohorts to evaluate the safety and PK to guide the selection of the **MTD** ~~RP2D~~ of GSK2636771. Dosing decisions will be based on all available data at the end of each DLT reporting period (the first 28 days of combination treatment). Decisions for dose determination for subsequent cohorts will be documented and maintained by each site and in the GSK Trial Master Files (TMF).

In the Dose Expansion Phase, subjects will be assigned to receive GSK2636771 at doses identified at or below the MTD in the Dose Escalation Phase while continuing treatment with enzalutamide to evaluate the long-term safety of the combination as well as the 12-week non-PD rate. **This may include multiple dose levels in order to establish the RP2D of the combination treatment at the conclusion of combination treatment in any dose level.**

Clinical Response Assessments: The determination of clinical response, including disease progression, will be assessed by the PCWG2 criteria (see Section 8.8.2). The assessment of the 12 week non-PD-rate ~~in the Dose Expansion Phase~~will also be determined by ~~2~~PCWG2 criteria (either by RECIST 1.1, PSA progression, and/or progression in bone).

Section 3.3 – Discussion of Study Design:

Rationale for change:

Updated citation in the body of the text and added the citation in the Reference section.

Previous text:

The dosing of enzalutamide will be administered at the US FDA approved dose (refer to the Prescribing Information for enzalutamide [Xtandi, 2013]. Study treatment will continue until there is no longer clinical benefit (see Section 5.2), in the opinion of the investigator, or until an unacceptable AE (including stopping criteria outlined in Section 7.2), withdrawal of consent, permanent discontinuation of study treatment, or death occurs. Investigators will use the PCWG2 criteria to determine clinical response to each treatment.

Revised text:

The dosing of enzalutamide will be administered at the US FDA approved dose (refer to the Prescribing Information for enzalutamide [Xtandi, 201~~3~~**6**]. Study treatment will continue until there is no longer clinical benefit (see Section 5.2), in the opinion of the investigator, or until an unacceptable AE (including stopping criteria outlined in Section 7.2), withdrawal of consent, permanent discontinuation of study treatment, or death occurs. Investigators will use the PCWG2 criteria to determine clinical response to each treatment.

Section 3.4 Dose Escalation Phase:

Rationale for Change:

Due to possibility of multiple doses being explored in dose expansion, updated wording to clarify dose escalation population and how maximum tolerated dose will be defined.

Previous text:

In the Dose Escalation Phase, the dose of GSK2636771 will follow a modified 3+3 dose escalation procedure to evaluate the safety and PK for each combination dose level and to guide selection of the RP2D of the combination.

Revised text:

In the Dose Escalation Phase, the dose of GSK2636771 will follow a modified 3+3 dose escalation procedure to evaluate the safety and PK for each combination dose level and to guide selection of the ~~RP2D of the~~ combination **dose for dose expansion**.

Sections 3.4.5, 3.5 and Section 3.6 (new section) – Recommended Phase II dose/Dose Expansion Phase:

Rationale for change:

Due to possibility of multiple doses being explored in dose expansion, updated wording to clarify dose escalation population and how maximum tolerated dose will be defined. Movement of Section 3.4.5. under new section 3.6, thereby updated all remaining Section 3 heading numbers.

Previous text:

Section 3.4.5 Recommended Phase II Dose

The RP2D will be considered the lowest dose of GSK2636771 explored (at or below MTD) in the Dose Escalation Phase that provides adequate PK exposure and biologic activity with a superior tolerability profile.

Section 3.5 Dose Expansion Phase

Enrollment in the Dose Expansion Phase of the study may begin once the MTD and RP2D have been determined in the Dose Escalation Phase. Up to 20 additional subjects may be enrolled to better characterize the safety profile, PK, and clinical activity of the recommended doses of the combination of GSK2636771 + enzalutamide for future studies. One or more combination doses may be explored in the Dose Expansion Phase based the MTD and RP2D identified in the Dose Escalation Phase of the study.

In the Dose Expansion Phase, final analyses will occur 6 months after the last subject is enrolled to allow for adequate collection of safety information. Those subjects that have not completed the treatment phase of the study (see Section 5.2) at the time of the final analysis may be transferred to a continued access study, if available.

Revised text:

~~**Section 3.4.5 Recommended Phase II Dose**~~

~~The RP2D will be considered the lowest dose of GSK2636771 explored (at or below MTD) in the Dose Escalation Phase that provides adequate PK exposure and biologic activity with a superior tolerability profile.~~

Section 3.5 Dose Expansion Phase

Enrollment in the Dose Expansion Phase of the study may begin once **a suspected** ~~the~~ MTD ~~and RP2D~~ has~~ve~~ been determined in the Dose Escalation Phase. Up to 20 additional subjects **per dose level** may be enrolled to better characterize the safety profile, PK, and clinical activity of the recommended doses of the combination of GSK2636771 + enzalutamide for future studies. One or more combination doses may be explored in the Dose Expansion Phase based **on** the MTD ~~and RP2D~~ identified in the Dose Escalation Phase of the study. **To fully evaluate additional combination doses, up to 20 additional subjects per dose level may be enrolled**.

In the Dose Expansion Phase, final analyses will occur 6 months after the last subject is enrolled to allow for adequate collection of safety information. Those subjects that have not completed the treatment phase of the study (see Section 5.2) at the time of the final analysis may be transferred to a continued access study, if available.

Section 3.6 Recommended Phase II Dose

The RP2D will be considered the lowest dose of GSK2636771 explored (at or below MTD) in the Dose Escalation Phase that provides adequate PK exposure and biologic activity with a superior tolerability profile. **If multiple dose levels are explored in dose expansion, the RP2D will be based on the totality of data.**

Section 3.7.1 – Evaluation of Futility:

Rationale for Change:

Update of timing of futility analysis to occur when adequate subjects are enrolled. Update to the efficacy endpoint wording used for futility predictive probability design.

Previous text:

Futility will be evaluated in the Dose Expansion Phase of the study. The methodology is based on the predictive probability of success if enrollment continues to 20 subjects [Lee, 2008]. The predictive probability design is similar to a Green-Dahlberg design in that it allows for early stopping for futility. The differences are that the predictive probability design allows for evaluation of stopping rules after each subject, rather than at only two stages, once a minimum number of subjects are evaluable. In this particular study, we will stop only for futility. While the two designs have similar type I and type II error rates, the probability of early termination is greater with the predictive probability design.

Number of Subjects Enrolled	≤ This Number of Responses[1] to Stop Early for Futility
10	0
11	0
12	0
13	0
14	0
15	0
16	1
17	1
18	1
19	1
20	2

Abbreviation: PCWG2, Prostate Cancer Working Group 2; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors

1. Response for the purpose of futility is defined as lack of disease progression at 12 weeks according to PCWG2 criteria (either by RECIST 1.1, PSA progression and/or progression in bone).

Revised text:

Futility will be evaluated **when there is adequate enrollment** ~~in the Dose Expansion Phase of the study~~. The methodology **for evaluation of futility** is based on the predictive probability of success if enrollment continues to 20 subjects **per dose level** [Lee, 2008] ~~per dose level~~. The predictive probability design is similar to a Green-Dahlberg design in that it allows for early stopping for futility. The differences are that the predictive probability design allows for evaluation of stopping rules after each subject, rather than at only two stages, once a minimum number of subjects are evaluable. In this particular study, we will stop only for futility. While the two designs have similar type I and type II error rates, the probability of early termination is greater with the predictive probability design.

Number of Subjects Enrolled	≤ This Number of Responses[1] to Stop Early for Futility
10	0
11	0
12	0
13	0
14	0
15	0
16	1
17	1
18	1
19	1
20	2

Abbreviations: PCWG2, Prostate Cancer Working Group 2; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors

1. Response for the purpose of futility is defined as lack of disease progression at 12 weeks according to PCWG2 criteria. ~~(either by RECIST 1.1, PSA progression and/or progression in bone).~~**PSA progression in subjects with baseline radiological or bone disease will require RECIST or bone progression in addition to PSA progression to be determined a disease progressor.**

Section 4.1.1. – Number of Subjects:

Rationale for Change:

Updated of the potential number of subjects due to possibility of multiple dose expansion cohorts and clarification of wording due to combination of dose escalation and expansion populations.

Previous text:

A total of approximately 44 subjects will be enrolled in this study.

Dose Expansion Phase: In the Dose Expansion Phase, it is estimated that approximately 20 subjects will be enrolled, with evaluation for futility after the first 10 subjects have completed 12 weeks of treatment (see Section 3.7.1).

The sample size planned for the Dose Expansion Phase is not driven by statistical considerations as the cohort is meant to further understand the safety implications of enrolling subjects to combination therapy for an extended period of time. See Section 13.2 for sample size assumptions.

Revised text:

A total of **between** approximately 44 **and 64** subjects will be enrolled in this study**.**

Dose Expansion Phase: In the Dose Expansion Phase, it is estimated that approximately 20 subjects will be enrolled, with evaluation for futility after the first 10 subjects have completed 12 weeks of treatment (see Section 3.7.1). **This analysis may occur using the combination of the dose escalation and dose expansion population. If multiple dose levels of GSK2636771 are examined during dose expansion to establish the RP2D, each dose level cohort will enrol approximately 20 subjects, increasing the overall number of subjects targeted for enrolment in this study.**

~~The sample size planned for the Dose Expansion Phase is not driven by statistical considerations as the cohort is meant to further understand the safety implications of enrolling subjects to combination therapy for an extended period of time. See Section 13.2 for sample size assumptions.~~

Section 4.1.2. - Inclusion Criteria

Rationale for change:

Updated citation in the body of the text and added the citation in the Reference section.

Previous text:

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on GSK2636771 or enzalutamide that may impact subject eligibility is provided in the IB for GSK2636771 [GlaxoSmithKline Document Number 2011N117133_01] and the Prescribing Information for enzalutamide [Xtandi, 2013].

Revised text:

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on GSK2636771 or enzalutamide that may impact subject eligibility is provided in the IB for GSK2636771 [GlaxoSmithKline Document Number 2011N117133_01] and the Prescribing Information for enzalutamide [Xtandi, 201~~3~~**6**].

Section 4.1.2. - Inclusion Criteria 11:

Rationale for Change:

Due to updated changes for calcium and bone markers adjusted the Other section of the tests in this criteria and updated footnote, by adding footnote 6.

Previous text:

Other	
Serum Phosphate[6]	WNL
Serum Calcium (corrected)	WNL

6.Per CTCAE v4.0, Grade 1 hypophosphatemia is <LLN – 2.5 mg/dL (<LLN - 0.8 mmol/L

Revised text:

Other	
Serum Phosphate[6]	WNL
Serum Calcium[6] (corrected)	
Ionized Calcium[6]	WNL
Vitamin D[6]: 25-OH D and	**WNL**
1,25-OH2 D	**WNL**

6. ~~Per CTCAE v4.0, Grade 1 hypophosphatemia is <LLN – 2.5 mg/dL (<LLN – 0.8 mmol/L~~ Vitamin D supplementation may be added to achieve values WNL. Calcium supplements should be added for subjects with calcium values near the lower normal limit.

Section 6.1 – GSK2636771 GSK Investigational Product

Rationale for Change:

In the event that there are legal changes to the way that GSK2636771 is interpreted, added additional wording to include this possibility.

Previous text:

The contents of the label will be in accordance with all applicable regulatory requirements.

Revised text:

The contents of the label will be in accordance with all applicable regulatory **and/or legal** requirements.

Section 6.3.2. – Enzalutamide

Rationale for Change:

Updated citation in the body of the text and added the citation in the Reference section.

Previous text:

Per the product prescribing information for enzalutamide [Xtandi, 2013], the recommended dose of enzalutamide 160 mg (four 40 mg capsules) taken orally once daily will be administered during this study.

Revised text:

Per the product prescribing information for enzalutamide [Xtandi, 201~~3~~**6**], the recommended dose of enzalutamide 160 mg (four 40 mg capsules) taken orally once daily will be administered during this study.

Section 7.3.1 – Renal Insufficiency or Other Renal Events

Rationale for Change:

Based on emerging data and additional internal review, section adjusted and revised to adjust calcium management.

Previous text:

Prior to start of study treatment, concomitant medications should be reviewed for the potential risk of inducing nephrotoxicity and concomitant medications should be modified if clinically possible.

Close monitoring of serum creatinine, calcium and phosphate and treatment interruption for increased serum creatinine >2 mg/dL (or >0.5 mg/dL above baseline), hypocalcemia, and hypophosphatemia, respectively, should occur. Nephrology consultation should also be considered.

Guidelines regarding the management of renal insufficiency or renal-related events considered to be related to study treatment are provided in Table 10.

Table 10 Management and Dose Modifications for Renal Events

Hypocalcemia (serum calcium ≥Grade 2) ***or*** Hypophosphatemia (serum phosphate ≥Grade 3 or symptomatic Grade 2)	• Repeat serum calcium or phosphate level within 24 hrs of previous result
	  • If repeat value confirms Grade 2 serum calcium, or symptomatic Grade 2 serum phosphate.
	  • Immediately interrupt treatment with GSK2636771
	  • Treat as clinically indicated by local institutional standards
	  • Obtain serum PTH level
	  • Obtain blood sample for PK analysis, if requested (see SRM), within 24-72 hrs after the last dose (refer to Section 8.7.3.1 for details on PK sample collection)
	  • Obtain urine samples for urine creatinine, calcium, phosphate, and protein at treatment interruption; repeat every 7 days
	  • Repeat serum calcium or phosphate level every 7 days or more frequently if clinically indicated
	• If serum calcium fails to improve to Grade 1 or if serum phosphate fails to improve to asymptomatic Grade 2 within 14 days following dose interruption:
	  • Permanently discontinue treatment with GSK2636771
	  • Consult with GSK Medical Monitor
	• If serum calcium improves to Grade 1 or serum phosphate improves to asymptomatic Grade 2 or baseline, whichever is more improved within 14 days following dose interruption:
	  • Restart treatment with GSK2636771 with dose reduced by one dose level
	  • Repeat serum calcium or phosphate level per Time and Events Tables (Section 8.1) or more frequently if clinically indicated
	• If decreased serum calcium or phosphate levels reoccurs after one dose reduction :
	  • Repeat serum calcium or phosphate levels within 24 hrs to confirm

	result • If repeat serum calcium or phosphate levels confirm decrease, withdraw subject from treatment/study unless there is agreement between investigator and GSK Medical Monitor that subject will benefit from continued treatment following recovery of serum calcium or phosphate to baseline with dose of GSK2636771 further reduced one dose level. • If repeat serum calcium or phosphate fails to confirm a decrease, continue treatment with GSK2636771 at same dose level without interruption

Revised text:

Prior to start of study treatment, concomitant medications should be reviewed for the potential risk of inducing nephrotoxicity and concomitant medications should be modified if clinically possible.

Close monitoring of serum creatinine, calcium and phosphate and treatment interruption for increased serum creatinine >2 mg/dL (or >0.5 mg/dL above baseline), hypocalcemia, and hypophosphatemia, respectively, should occur. Nephrology consultation should also be considered.

Calcium should be carefully managed in all subjects and especially in subjects with bone lesions/metastases and in those on treatments that are associated with hypocalcemia, including but not limited to, bisphosphanates (e.g., zoledronic acid) or denosumab (RANK-L inhibitor). Subjects with baseline calcium levels at or near the lower normal limit and those with Vitamin D below the normal limit should be treated with supplements. Subjects who develop hypocalcemia should be closely monitored and managed per Table 10.

Guidelines regarding the management of renal insufficiency or renal-related events considered to be related to study treatment are provided in Table 10.

Management and Dose Modifications for Renal Events

Hypocalcemia (serum calcium ≥Grade ~~2~~**1**)
or
Hypophosphatemia (serum phosphate ≥Grade 3 or symptomatic Grade 2)
	• **Administration of oral calcium supplements to subjects with calcium levels at or near the lower limit of normal should be considered**
	• **For subjects with Grade1 hypocalcemia, administer oral calcium supplements and evaluate the need for Vitamin D supplementation.**
	• **For hypocalcemia > Grade 1,** ~~R~~**r**epeat serum calcium **and Vitamin D,and** ~~or~~ phosphate level within 24 hrs of previous result
	  • If repeat value confirms **>** Grade ~~2~~**1** serum calcium, or symptomatic Grade 2 serum phosphate.
	  • Immediately interrupt treatment with GSK2636771
	  • Treat as clinically indicated by local institutional standards **or administer i.v. calcium gluconate (1 g/10 ml) and evaluate the need for Vitamin D supplementation.**
	  • Obtain serum PTH level
	  • Obtain blood sample for PK analysis, if requested (see SRM), within 24-72 hrs after the last dose (refer to Section 8.7.3.1 for details on PK sample collection)

	• Obtain urine samples for urine creatinine, calcium, phosphate, and protein at treatment interruption; repeat every 7 days • Repeat serum calcium or phosphate level every 7 days or more frequently if clinically indicated • If serum calcium fails to improve to ~~Grade 1~~ **WNL** or if serum phosphate fails to improve to asymptomatic Grade 2 within 14 days following dose interruption: • Permanently discontinue treatment with GSK2636771 • Consult with GSK Medical Monitor • If serum calcium improves to ~~Grade 1~~ **WNL** or serum phosphate improves to asymptomatic Grade 2 ~~or baseline, whichever is more improved~~ within 14 days following dose interruption: • Restart treatment with GSK2636771 with dose reduced by one dose level • Repeat serum calcium or phosphate level per Time and Events Tables (Section 8.1) or more frequently if clinically indicated • If decreased serum calcium or phosphate levels reoccurs after one dose reduction : • Repeat serum calcium or phosphate levels within 24 hrs to confirm result • If repeat serum calcium or phosphate levels confirm decrease, withdraw subject from treatment/study unless there is agreement between investigator and GSK Medical Monitor that subject will benefit from continued treatment following recovery of serum calcium or phosphate to baseline with dose of GSK2636771 further reduced one dose level. • If repeat serum calcium or phosphate fails to confirm a decrease, continue treatment with GSK2636771 at same dose level without interruption

Section 8.1 – Time and Events Tables

Rationale for Changes:

Visit window clarifications at Week 1, Day 1and Week 12 to clarify that assessments are to occur only after that visit timeframe has passed; updates to laboratory assessments section including additional footnotes 33, 34 and 35; update to footnotes 12 and 15.

Previous text:

Table 15 Time and Events Table for Dose Escalation Phase

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**		**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression[31]**	**Post-Treatment Follow-Up Visit[28]**	**Extended Follow-Up Visits[29]**	**Post-Extended Follow-Up /EOS Visit[30]**
		Day -14 to Day -1	Day 1 to Day 13	Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Wk 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window					*±1 day*	*±1 day*	*±1 day*	*±1 day*	*±1 day*	*±3 days for each visit*	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Clinical Assessments														
Informed Consent	X[3]	X[4]												
Demographics	X													
Medical History		X												
Determination of PTEN Deficiency Status	M[5]													
Safety Assessments														
ECOG PS		X			X		X	X	X	Week 8 and then Q8wks	X	X		X
Physical Exam		X			X					Week 8 and then Q8wks		X		X
Height[8]		X												
Weight		X			X					Week 8 and then Q8wks		X		X
Vital Signs[9]		X			X	X	X	X	X	X		X		X
12-Lead ECG[10]		X[6]						X		Week 8 and then Q8wks		X		X
ECHO/MUGA		X[6,7]			As clinically indicated									
AE Monitoring			Continuous								X[11]	X[11]		

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**		**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression**[31]	**Post-Treatment Follow-Up Visit**[28]	**Extended Follow-Up Visits**[29]	**Post-Extended Follow-Up /EOS Visit**[30]
		Day -14 to Day -1	Day 1 to Day 13	Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Wk 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window					*±1 day*	*±1 day*	*±1 day*	*±1 day*	*±1 day*	*±3 days for each visit*	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Concomitant Medications		X	Continuous									X		
Laboratory Assessments[12]														
Hematology/ Clinical Chemistry		X[6]			X	X	X	X	X	X		X		X
Coagulation: PT, PTT, INR		X[6]			X			X						
Liver Function Tests		X[6]			X	X	X	X	X	X		X		X
Urinalysis[13] Urine Microscopy[13] UPC[14]		X[6]			X			X		X		X		X
Urine Electrolytes[15]		X[6]			X		X	X		Week 8 and then Q8wks		X		
Parathyroid Hormone					X	As clinically indicated[16]								
Laboratory Assessments *continued*														
PSA and LDH[32]		X[6]			X					X	X	X		X
Serum Testosterone		X[6]										X		X
PK Assessments														
PK Blood Sampling[17]				X					X	Weeks 8 and 12				
Disease Assessments[18]														

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**		**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression**[31]	**Post-Treatment Follow-Up Visit**[28]	**Extended Follow-Up Visits**[29]	**Post-Extended Follow-Up /EOS Visit**[30]
		Day -14 to Day -1	Day 1 to Day 13	Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Wk 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window					*±1 day*	*±1 day*	*±1 day*	*±1 day*	*±1 day*	*±3 days for each visit*	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
CT Scan or MRI[19]		X[6,7]								Week 8 and then Q8wks to Week 48; then Q12wks	X		X	
Chest X-Ray or Chest CT Scan		X[6,7]												
Bone Scan[20]		X[6,7]								Week 12 and then Q12wks	X		X	
Biomarker Assessments														
CTC –- Janssen[21]		X			X			X		Weeks 8, 16, 24, and 32	X			
CTC – EPIC[22]		X								Week 8 only	X			
Biomarker Assessments *continued*														
Predictive Biomarker: Tumor Tissue[23]					X									
Progression Tumor yBiopsy[24]											X			
Tumor Biopsies for Pharmaco-dynamics[24]				X		X[24]								
cfDNA/RNA/Soluble Markers[25]		X			X			X		Weeks 8, 16, 24, and 32	X			
Blood Sample for Genetic Research[26]					X									

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**		**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression[31]**	**Post-Treatment Follow-Up Visit[28]**	**Extended Follow-Up Visits[29]**	**Post-Extended Follow-Up /EOS Visit[30]**
		Day -14 to Day -1	Day 1 to Day 13	Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Wk 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window					*±1 day*	*±1 day*	*±1 day*	*±1 day*	*±1 day*	*±3 days for each visit*	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Study Treatments[27]														
Enzalutamide			Continuous		Continuous									
GSK2636771					Continuous									

12. Laboratory Assessments: Refer to Section 8.6.5 for list of specific laboratory tests to be performed. Assessments may be performed within 24 hrs prior to scheduled visit (liver function tests and urine tests for UPC may be performed up to 72 hrs prior to a scheduled visit) to ensure availability of results.

15. Urine Electrolytes: Urine samples will be obtained at Screening, pre-dose on Day 1 (Week 1), Day 15 (Week 3), Day 22 (Week 4) of the Combination Treatment Period, Week 8 and then every 8 weeks (± 3 days) thereafter during the Treatment Continuation Period, and at the post-treatment follow-up visit to determine urine electrolytes (magnesium, phosphorus and calcium) and urine creatinine.

Revised text:

Table 15 Time and Events Table for Dose Escalation Phase

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**		**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression[31]**	**Post-Treatment Follow-Up Visit[28]**	**Extended Follow-Up Visits[29]**	**Post-Extended Follow-Up /EOS Visit[30]**
		Day -14 to Day -1	Day 1 to Day 13	Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Wk 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window					***+±1 day***	*±1 day*	*±1 day*	*±1 day*	*±1 day*	***+5 days Week 12 only;*** *±3 days* ***for all other visits*** ~~*for each visit*~~	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Clinical Assessments														
Informed Consent	X[3]	X[4]												
Demographics	X													
Medical History		X												
Determination of PTEN Deficiency Status	M[5]													
Safety Assessments														
ECOG PS		X			X		X	X	X	Week 8 and then Q8wks	X	X		X
Physical Exam		X			X					Week 8 and then Q8wks		X		X
Height[8]		X												
Weight		X			X					Week 8 and then Q8wks		X		X
Vital Signs[9]		X			X	X	X	X	X	X		X		X
12-Lead ECG[10]		X[6]						X		Week 8 and then		X		X

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**		**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression**[31]	**Post-Treatment Follow-Up Visit**[28]	**Extended Follow-Up Visits**[29]	**Post-Extended Follow-Up /EOS Visit**[30]
		Day -14 to Day -1	Day 1 to Day 13	Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Wk 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window					**+**±*1 day*	±*1 day*	±*1 day*	±*1 day*	±*1 day*	***+5 days Week 12 only;*** ±*3 days* ***for all other visits*** ~~*for each visit*~~	*+1 day*	*-2/+7 days*	±*14 days*	±*3 days*
										Q8wks				
ECHO/MUGA		X[6,7]			As clinically indicated									
AE Monitoring			Continuous								X[11]	X[11]		
Concomitant Medications		X	Continuous									X		
Laboratory Assessments[12]														
Hematology/ Clinical Chemistry		X[6]			X[33]	X	X	X	X	X		X		X
Ionized Calcium		**X**[6]			**X**	**X**	**X**	**X**	**X**	**X**		**X**		**X**
Vitamin D[34]		**X**[6]						**X**				**X**		**X**
Coagulation: PT, PTT, INR		X[6]			X			X						
Liver Function Tests		X[6]			X	X	X	X	X	X		X		X
Urinalysis[13] Urine Microscopy[13] UPC[14]		X[6]			X			X		X		X		X
Urine Electrolytes[15]		X[6]			X[33]	**X**	X	X		Week 8 and then Q8wks		X		
Parathyroid Hormone					X	As clinically indicated[16]								

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**		**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression[31]**	**Post-Treatment Follow-Up Visit[28]**	**Extended Follow-Up Visits[29]**	**Post-Extended Follow-Up /EOS Visit[30]**
		Day -14 to Day -1	Day 1 to Day 13	Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Wk 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window					**+**±*1 day*	±*1 day*	±*1 day*	±*1 day*	±*1 day*	***+5 days Week 12 only;*** ±*3 days* ***for all other visits*** ~~*for each visit*~~	*+1 day*	*-2/+7 days*	±*14 days*	±*3 days*
Bone Markers[35]					**X**				**X**	**Weeks 12 and 24**		**X**		**X**
Laboratory Assessments *continued*														
PSA and LDH[32]		X[6]			X					X	X	X		X
Serum Testosterone		X[6]										X		X
PK Assessments														
PK Blood Sampling[17]				X					X	Weeks 8 and 12				
Disease Assessments[18]														
CT Scan or MRI[19]		X[6,7]								Week 8 and then Q8wks to Week 48; then Q12wks	X		X	
Chest X-Ray or Chest CT Scan		X[6,7]												
Bone Scan[20]		X[6,7]								Week 12 and then Q12wks	X		X	
Biomarker Assessments														
CTC –- Janssen[21]		X			X			X		Weeks 8, 16, 24, and 32	X			
CTC – EPIC[22]		X								Week 8 only	X			

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**		**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression**[31]	**Post-Treatment Follow-Up Visit**[28]	**Extended Follow-Up Visits**[29]	**Post-Extended Follow-Up /EOS Visit**[30]
		Day -14 to Day -1	Day 1 to Day 13	Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Wk 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window					**+~~±~~*1 day*	*±1 day*	*±1 day*	*±1 day*	*±1 day*	***+5 days Week 12 only;** ±3 days **for all other visits** ~~*for each visit*~~*	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Biomarker Assessments *continued*														
Predictive Biomarker: Tumor Tissue[23]					X									
Progression Tumor Biopsy[24]											X			
Tumor Biopsies for Pharmaco-dynamics[24]				X		X[24]								
cfDNA/RNA/Soluble Markers[25]		X			X			X		Weeks 8, 16, 24, and 32	X			
Blood Sample for Genetic Research[26]					X									
Study Treatments[27]														
Enzalutamide			Continuous		Continuous									
GSK2636771					Continuous									

12. Laboratory Assessments: Refer to Section **8.6.6~~8.6.5~~ (Table 17**) for list of specific laboratory tests to be performed. Assessments may be performed within 24 hrs prior to scheduled visit (liver function tests and urine tests for UPC may be performed up to 72 hrs prior to a scheduled visit) to ensure availability of results.

15.Urine Electrolytes: Urine samples will be obtained at Screening, pre-dose on Day 1 (Week 1), **Day 3 OR Day 4,** Day 15 (Week 3), Day 22 (Week 4) of the Combination Treatment Period, Week 8 and then every 8 weeks (± 3 days) thereafter during the Treatment Continuation Period, and at the post-treatment follow-up visit to determine urine electrolytes (magnesium, phosphorus and calcium) and urine creatinine.

33.Complete clinical chemistries laboratory assessments at Week1/Day 1 and again on either Day 3 or Day 4. The Day 3 or Day 4 assessments can be completed at a local laboratory and does not require a clinic visit. The hematology panel does NOT need to be collected on Day 3/ Day 4. Review of these labs must occur before Week 2, Day 1 visit.

34.Includes assessments for 25-OH D and 1,25-OH2 D.

35.Includes urine and blood and/or serum samples. Must be collected at the same time of day (±1 hour) to eliminate diurnal effects, and after fasting. See SRM for additional details on the specific assessments and sample collection.

Previous text:

Table 16 Time and Events Table for Dose Expansion Phase

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**	**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression**[31]	**Post-Treatment Follow-Up Visit**[28]	**Extended Follow-Up Visits**[29]	**Post-Extended Follow-Up /EOS Visit**[30]
		Day -14 to Day -1	Day 1 to Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Wk 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window				*±1 day*	*±1 day*	*±1 day*	*±1 day*	*±1 day*	*±3 days for each visit*	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Clinical Assessments													
Informed Consent	X[3]	X[4]											
Demographics	X												
Medical History		X											
Determination of PTEN Deficiency Status	M[5]												
Safety Assessments													
ECOG PS		X		X		X	X	X	Week 8 and then Q8wks	X	X		X

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**	**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression**[31]	**Post-Treatment Follow-Up Visit**[28]	**Extended Follow-Up Visits**[29]	**Post-Extended Follow-Up /EOS Visit**[30]
		Day -14 to Day -1	Day 1 to Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Wk 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window				*±1 day*	*±1 day*	*±1 day*	*±1 day*	*±1 day*	*±3 days for each visit*	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Physical Exam		X		X					Week 8 and then Q8wks		X		X
Height[8]		X											
Weight		X		X					Week 8 and then Q8wks		X		X
Vital Signs[9]		X		X	X	X	X	X	X		X		X
12-Lead ECG[10]		X[6]					X		Week 8 and then Q8wks		X		X
ECHO/MUGA		X[6,7]		As clinically indicated									
AE Monitoring			Continuous							X[11]	X[11]		
Concomitant Medications		X	Continuous								X		
Laboratory Assessments[12]													
Hematology/ Clinical Chemistry		X[6]		X	X	X	X	X	X		X		X
Coagulation: PT, PTT, INR		X[6]		X			X						
Liver Function Tests		X[6]		X	X	X	X	X	X		X		X
Urinalysis[13] Urine Microscopy[13] UPC[14]		X[6]		X			X		X		X		X
Urine Electrolytes[15]		X[6]		X		X	X		Week 8 and then Q8wks		X		

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**	**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression[31]**	**Post-Treatment Follow-Up Visit[28]**	**Extended Follow-Up Visits[29]**	**Post-Extended Follow-Up /EOS Visit[30]**
		Day -14 to Day -1	Day 1 to Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Wk 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window				*±1 day*	*±1 day*	*±1 day*	*±1 day*	*±1 day*	*±3 days for each visit*	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Parathyroid Hormone				X	As clinically indicated[16]								
Laboratory Assessments *continued*													
PSA and LDH[32]		X[6]		X					X	X	X		X
Serum Testosterone		X[6]									X		X
PK Assessments													
PK Blood Sampling[17]								X	Weeks 8 and 12				
Disease Assessments[18]													
CT Scan or MRI[19]		X[6,7]							Week 8 and then Q8wks to Week 48; then Q12wks	X		X	
Chest X-Ray or Chest CT Scan		X[6,7]											
Bone Scan[20]		X[6,7]							Week 12 and then Q12wks	X		X	
Biomarker Assessments													
CTC –- Janssen[21]		X		X			X		Weeks 8, 16, 24, and 32	X			
CTC – EPIC[22]		X							Week 8 only	X			
Biomarker Assessments *continued*													
Predictive				X									

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**	**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression**[31]	**Post-Treatment Follow-Up Visit**[28]	**Extended Follow-Up Visits**[29]	**Post-Extended Follow-Up /EOS Visit**[30]
		Day -14 to Day -1	Day 1 to Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Wk 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window				*±1 day*	*±1 day*	*±1 day*	*±1 day*	*±1 day*	*±3 days for each visit*	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Biomarker: Tumor Tissue[23]													
Progression Tumor yBiopsy[24]										X			
Tumor Biopsies for Pharmaco-dynamics[24]			X (Day 14)		X[24]								
cfDNA/RNA/Soluble Markers[25]		X		X			X		Weeks 8, 16, 24, and 32	X			
Blood Sample for Genetic Research[26]				X									
Study Treatments[27]													
Enzalutamide			Continuous	Continuous									
GSK2636771				Continuous									

12.Laboratory Assessments: Refer to Section 8.6.5 for list of specific laboratory tests to be performed. Assessments may be performed within 24 hrs prior to scheduled visit (liver function tests and urine tests for UPC may be performed up to 72 hrs prior to a scheduled visit) to ensure availability of results.

15.Urine Electrolytes: Urine samples will be obtained at Screening, pre-dose on Day 1 (Week 1), Day 15 (Week 3), Day 22 (Week 4) of the Combination Treatment Period, Week 8 and then every 8 weeks (± 3 days) thereafter during the Treatment Continuation Period, and at the post-treatment follow-up visit to determine urine electrolytes (magnesium, phosphorus and calcium) and urine creatinine.

Revised text:

Table 16 Time and Events Table for Dose Expansion Phase

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**		**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression[31]**	**Post-Treatment Follow-Up Visit[28]**	**Extended Follow-Up Visits[29]**	**Post-Extended Follow-Up /EOS Visit[30]**
		Day -14 to Day -1	Day 1 to Day 13	Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Wk 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window					***+±1 day***	*±1 day*	*±1 day*	*±1 day*	*±1 day*	***+5 days Week 12 only;*** *±3 days* ***for all other visits*** ~~*for each visit*~~	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Clinical Assessments														
Informed Consent	X[3]	X[4]												
Demographics	X													
Medical History		X												
Determination of PTEN Deficiency Status	M[5]													
Safety Assessments														
ECOG PS		X			X		X	X	X	Week 8 and then Q8wks	X	X		X
Physical Exam		X			X					Week 8 and then Q8wks		X		X
Height[8]		X												
Weight		X			X					Week 8 and then Q8wks		X		X
Vital Signs[9]		X			X	X	X	X	X	X		X		X
12-Lead ECG[10]		X[6]						X		Week 8 and then		X		X

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**		**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression[31]**	**Post-Treatment Follow-Up Visit[28]**	**Extended Follow-Up Visits[29]**	**Post-Extended Follow-Up /EOS Visit[30]**
		Day -14 to Day -1	Day 1 to Day 13	Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Wk 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window					**+**±*1 day*	±*1 day*	±*1 day*	±*1 day*	±*1 day*	***+5 days Week 12 only;*** ±*3 days* ***for all other visits*** ~~*for each visit*~~	*+1 day*	*-2/+7 days*	±*14 days*	±*3 days*
										Q8wks				
ECHO/MUGA		X[6,7]			As clinically indicated									
AE Monitoring			Continuous								X[11]	X[11]		
Concomitant Medications		X	Continuous									X		
Laboratory Assessments[12]														
Hematology/ Clinical Chemistry		X[6]			X[33]	X	X	X	X	X		X		X
Ionized Calcium		**X[6]**			**X**	**X**	**X**	**X**	**X**	**X**		**X**		**X**
Vitamin D[34]		**X[6]**						**X**				**X**		**X**
Coagulation: PT, PTT, INR		X[6]			X			X						
Liver Function Tests		X[6]			X	X	X	X	X	X		X		X
Urinalysis[13] Urine Microscopy[13] UPC[14]		X[6]			X			X		X		X		X
Urine Electrolytes[15]		X[6]			X[33]	**X**	X	X		Week 8 and then Q8wks		X		
Parathyroid Hormone		**X**			~~X~~	As clinically indicated[16]						**X**		

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**		**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression[31]**	**Post-Treatment Follow-Up Visit[28]**	**Extended Follow-Up Visits[29]**	**Post-Extended Follow-Up /EOS Visit[30]**
		Day -14 to Day -1	Day 1 to Day 13	Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Wk 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window					**+**±*1 day*	±*1 day*	±*1 day*	±*1 day*	±*1 day*	***+5 days Week 12 only;*** ±*3 days* ***for all other visits*** ~~*for each visit*~~	+*1 day*	-*2/+7 days*	±*14 days*	±*3 days*
Bone Markers[35]					**X**				**X**	**Weeks 12 and 24**		**X**		**X**
Laboratory Assessments *continued*														
PSA and LDH[32]		X[6]			X					X	X	X		X
Serum Testosterone		X[6]										X		X
PK Assessments														
PK Blood Sampling[17]				X					X	Weeks 8 and 12				
Disease Assessments[18]														
CT Scan or MRI[19]		X[6,7]								Week 8 and then Q8wks to Week 48; then Q12wks	X		X	
Chest X-Ray or Chest CT Scan		X[6,7]												
Bone Scan[20]		X[6,7]								Week 12 and then Q12wks	X		X	
Biomarker Assessments														
CTC –- Janssen[21]		X			X			X		Weeks 8, 16, 24, and 32	X			
CTC – EPIC[22]		X								Week 8 only	X			

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**		**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression**[31]	**Post-Treatment Follow-Up Visit**[28]	**Extended Follow-Up Visits**[29]	**Post-Extended Follow-Up /EOS Visit**[30]
		Day -14 to Day -1	Day 1 to Day 13	Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Wk 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window					**+~~±~~*1 day*	*±1 day*	*±1 day*	*±1 day*	*±1 day*	***+5 days Week 12 only;*** *±3 days* ***for all other visits*** ~~*for each visit*~~	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Biomarker Assessments *continued*														
Predictive Biomarker: Tumor Tissue[23]					X									
Progression Tumor Biopsy[24]											X			
Tumor Biopsies for Pharmaco-dynamics[24]				X		X[24]								
cfDNA/RNA/Soluble Markers[25]		X			X			X		Weeks 8, 16, 24, and 32	X			
Blood Sample for Genetic Research[26]					X									
Study Treatments[27]														
Enzalutamide			Continuous		Continuous									
GSK2636771					Continuous									

12.Laboratory Assessments: Refer to Section **8.6.6~~8.6.5~~ (Table 17)** for list of specific laboratory tests to be performed. Assessments may be performed within 24 hrs prior to scheduled visit (liver function tests and urine tests for UPC may be performed up to 72 hrs prior to a scheduled visit) to ensure availability of results.

15.Urine Electrolytes: Urine samples will be obtained at Screening, pre-dose on Day 1 (Week 1), **Day 3 OR Day 4,** Day 15 (Week 3), Day 22 (Week 4) of the Combination Treatment Period, Week 8 and then every 8 weeks (± 3 days) thereafter during the Treatment Continuation Period, and at the post-treatment follow-up visit to determine urine electrolytes (magnesium, phosphorus and calcium) and urine creatinine.

33.Complete clinical chemistries laboratory assessments at Week1/Day 1 and again on either Day 3 or Day 4. The Day 3 or Day 4 assessments can be completed at a local laboratory and does not require a clinic visit. The hematology panel does NOT need to be collected on Day 3/ Day 4. Review of these labs must occur before Week 2, Day 1 visit.

34.Includes assessments for 25-OH D and 1,25-OH2 D.

35.Includes urine and blood and/or serum samples. Must be collected at the same time of day (±1 hour) to eliminate diurnal effects, and after fasting. See SRM for additional details on the specific assessments and sample collection.

Section 8.6.6. – Laboratory Assessments

Rationale for Change:

Addition to Table of Laboratory Assessments of the new tests added to Other tests section of this amendment.

Previous text:

Other tests
PSA
Serum Testosterone
Coagulation Tests: PT/PTT/INR
Serum Parathyroid Hormone (PTH)

Revised text:

Other tests
PSA
Serum Testosterone
Coagulation Tests: PT/PTT/INR
Serum Parathyroid Hormone (PTH)
Ionized Calcium
25-OH D and 1,25-OH2 D
Bone Markers[5]

5..Refer to SRM

Section 8.8.2. – Disease Assessment

Rationale for Change:

Added text to clarify the importance of completing these Week 12 assessments at the appropriate time after the start of combination treatment.

Previous text:

The primary endpoint is to evaluate the 12 week non-PD rate of oral GSK2636771 + enzalutamide according to PCWG2 guidelines (either by RECIST 1.1, PSA progression, and/or progression in bone).

Revised text:

The primary endpoint is to evaluate the 12 week non-PD rate of oral GSK2636771 + enzalutamide according to PCWG2 guidelines (either by RECIST 1.1, PSA progression, and/or progression in bone). **These assessments at Week 12 should occur at least 12 weeks (+5 day window) after start of combination treatment.**

Section 8.8.2.1. – PSA Response per PCWG2 Criteria

Rationale for Change:

Adjusted the rate of PSA to include that PSA decrease can be equal to 50%.

Previous text:

PSA Response Rate is defined as proportion of subjects with a decrease of >50% in the PSA concentration from the baseline PSA value determined at least 12 weeks after start of treatment and confirmed after ≥4 weeks by an additional PSA evaluation.

Revised text:

PSA Response Rate is defined as proportion of subjects with a decrease of ≥~~>~~50% in the PSA concentration from the baseline PSA value determined at least 12 weeks after start of treatment and confirmed after ≥4 weeks by an additional PSA evaluation.

Section 8.8.2.2. – Radiographic Response per PCWG2 Criteria

Rationale for Change:

Revisions and additional wording to further clarify the bone progression definition.

Previous text:

Bone progression [Scher, 2008] is defined as the appearance of ≥2 new lesions on bone scan, and a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions. The date of progression is the date of the first scan that indicates the change. Subjects should not be discontinued from study treatment(s) due to the occurrence of bone scan changes in the first 12 weeks of combination treatment that do not meet PCWG2 guidelines for progression.

Revised text:

Bone progression [Scher, 2008] is defined as the appearance of ≥2 new lesions~~on bone scan~~**, and, for the first reassessment only,** a confirmatory **bone** scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions. **The first post-treatment bone scan (Week 12) will be used as the baseline scan with which all future bone scans are compared.** The date of progression is the date of the first scan that **shows a minimum of 2 additional new lesions** ~~indicates the change~~. Subjects should not be discontinued from study treatment(s) due to the occurrence of bone scan changes in the first 12 weeks of combination treatment that do not meet PCWG2 guidelines for progression.

Section 8.8.2.3. – Disease Progression Endpoint

Rationale for Change:

Revisions to clarify update to PSA progression assessment for inclusion in disease progression analysis.

Previous text:

PSA progression according to the PCWG2 criteria (Section 8.8.2.1)

Revised text:

- PSA progression according to the PCWG2 criteria (Section 8.8.2.1) **with accompanying progression by RECIST 1.1 or bone scan for subjects with measeurable baseline disease OR PSA progression if no measurable baseline disease**

Section 10.1 – Permitted Medications

Rationale for Change:

Revised Supportive Care section to allow the use of calcium supplements and Vitamin D supplements due to changes to inclusion minimums and management guidelines.

Previous text:

Supportive Care: Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, and other care as deemed appropriate, and in accordance with local institutional guidelines.

Revised text:

Supportive Care: Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, **calcium supplements, Vitamin D supplements,** and analgesics, and other care as deemed appropriate, and in accordance with local institutional guidelines.

Section 10.2.2. – Potential Drug Interactions with Enzalutamide

Rationale for Change:

Updated citation in the body of the text and added the citation in the Reference section.

Previous text:

The following information is provided as an initial reference, however, please refer to the approved US FDA prescribing information [Xtandi, 2013] or the Xtandi Prescribing Information for the area where it is approved for the most current DDI information and contraindicated medications.

Revised text:

The following information is provided as an initial reference, however, please refer to the approved US FDA prescribing information [Xtandi, 201~~3~~**6**] or the Xtandi Prescribing Information for the area where it is approved for the most current DDI information and contraindicated medications.

Section 13.1.2. – Dose Expansion Phase:

Rationale for Change:

Clarifications to Dose Expansion phase section to clarify that multiple doses may be examined.

Previous text:

For the Dose Expansion Phase, the hypothesized non-PD rate is provided in Section 13.2.2. In this case, a test that non-PD rate is less than or equal to the null hypothesis rate versus the non-PD rate is greater than or equal to the alternative rate is being performed using the stopping rules provided in Section 13.2.2. Descriptive statistics will be used to describe the response data at the RP2D dose used in the expanded cohort.

Revised text:

~~For the Dose Expansion Phase, t~~**T**he hypothesized non-PD rate is provided in Section 13.2.2. In this case, a test that non-PD rate is less than or equal to the null hypothesis rate versus the non-PD rate is greater than or equal to the alternative rate is being performed using the stopping rules provided in Section 13.2.2. Descriptive statistics will be used to describe the response data at the ~~RP2D~~ dose**(s)** used in the expanded cohort**(s).**

Section 13.2.2. – Dose Expansion Phase:

Rationale for Change:

Clarifications to Dose Expansion phase section to clarify that multiple doses may be examined.

Previous text:

An initial dose finding will be used to establish the RP2D for the combination arm. Once the final dose is confirmed, at least 10 subjects will be enrolled at the appropriate RP2D, using decision rules defined in Table 3. The sample size and stopping rules are based on the methodology of Lee [Lee, 2008].

Revised text:

An initial dose finding will be used to establish the ~~RP2D~~ MTD for the combination arm. Once the final dose is confirmed, at least 10 subjects will be enrolled at the appropriate dose level ~~RP2D~~, using decision rules defined in Table 3. The sample size and stopping rules are based on the methodology of Lee [Lee, 2008].

Section 13.3.1 – Analysis Populations

Rationale for Change:

Revised and added population to clarify between safety and clinical activity populations and to define the evaluable population for endpoint analyses.

Previous text:

All Treated Population: The All Treated Population is defined as all subjects who receive at least one dose of GSK2636771. This will be the main population for all analyses.

Pharmacokinetic (PK) Population: The PK Population will consist of all subjects from the All Treated Population for whom at least one PK sample is obtained and analyzed.

All Screened Population: The All Screened Population is defined as all subjects for whom pre-screening consent is obtained.

Revised text:

~~All Treated Population:~~ The **All Treated Safety Population** is defined as all subjects who receive at least one dose of GSK2636771 **or Enzalutamide**. ~~This will be the main population for all analyses~~. **Safety will be evaluated based on this analysis population.**

The All Treated Clinical Activity Population is defined as all subjects who received at least one dose of GSK2636771. Clinical activity and evaluation of non-PD rate will be based on this analysis population. This will include subjects from both dose escalation and dose expansion

The All Evaluable Population is defined as all subjects from All Treated Clinical Activity Population who have at least one post-dose disease assessment and have been exposed to study drug for at least 12 weeks or have progressed or have died or have withdrawn from the study for any reason. Dose Expansion futility analyses will be based on this population.

Pharmacokinetic (PK) Population: The PK Population will consist of all subjects from the All Treated Population for whom a PK sample is obtained and analyzed.

~~All Screened Population: The All Screened Population is defined as all subjects for whom pre-screening consent is obtained.~~

Section 13.3.3.2. – Dose Expansion Phase

Rationale for Change:

Clarification on futility analysis timeframe and population for this analysis.

Previous text:

After the initial 10 subjects have enrolled at the RP2D dose, 12-week non-PD rate will be reviewed on an ongoing basis and the number of responses observed will be compared with the stopping rules provided in Section 13.2.2.

Revised text:

After the initial 10 subjects ~~have enrolled at the RP2D~~ **become evaluable at a dose level using a combination of dose escalation and dose expansion subjects**, 12-week non-PD

rate will be reviewed on an ongoing basis and the number of responses observed will be compared with the stopping rules provided in Section 13.2.2.

Section 13.3.4.1 – Efficacy Analyses

Rationale for Change:

Updated of population to be used for analyses; added and revised secondary analyses.

Previous text:

The All Treated Population will be used for the analysis of efficacy data. Efficacy analyses will be provided separately for each cohort.

Primary Analyses

The primary analysis is to determine whether the 12-week non PD rate is greater than or equal to 5%. The 12-week non PD rate is defined as the percentage of subjects without progression at Week 12. Subjects with unknown or missing response will not be treated as not having PD (i.e., subjects with NE will be included in the denominator when calculating the percentage of non-PD). Non-PD rate will be provided along with corresponding exact 95% CIs.

Secondary Analyses

PSA and RECIST response data will be reported. Subjects with unknown or missing response data, including those who withdraw from the study without an assessment, will be treated as non-responders (i.e., they will be included in the denominator when calculating the percentage). No imputation will be performed for missing lesion assessment or tumor response data. An exact 95% CI will be computed for the PSA and RECIST response rate.

Revised text:

The All Treated **Clinical Activity** Population will be used for the analysis of efficacy data**, and will be summarized separately for each dose level combining data from both dose escalation and does expansion**. Efficacy analyses will be provided separately for each **dose level**~~cohort~~.

Primary Analyses

The primary analysis is to determine whether the 12-week non PD rate is greater than or equal to 5%. The 12-week non PD rate is defined as the percentage of subjects without progression at Week 12. **Progression is defined by RECIST 1.1 or progression in bone or PSA progression with accompanying progression by RECIST 1.1 or bone scan when baseline disease present or PSA progression solely if no other baseline disease.** Subjects with unknown or missing response will not be treated as not having PD (i.e., subjects with NE will be included in the denominator when calculating the percentage of non-PD). Non-PD rate will be provided along with corresponding exact 95% CIs.

Secondary Analyses

PSA and RECIST **1.1** response data will be reported. Subjects with unknown or missing response data, including those who withdraw from the study without an assessment, will be treated as non-responders (i.e., they will be included in the denominator when calculating the percentage). No imputation will be performed for missing lesion assessment or tumor response data. An exact 95% CI will be computed for the PSA**50 response rate** and RECIST **1.1 confirmed** response rate.

New text:

PSA Response Rate

PSA Response rate (RR) is defined as proportion of subjects with a decrease of ≥50% in the PSA concentration from the baseline PSA value determined at least 12 weeks after start of treatment and confirmed after ≥4 weeks by an additional PSA evaluation RR will be reported by dose level along with the exact 95% confidence interval. Waterfall plots will be presented that show the maximum percentage of change in PSA reduction from baseline.

Objective Response Rate

The objective response (ORR) rate is defined as the percentage of subjects with a confirmed complete response (CR) or a partial response (PR) at any time as per PCWG3-modified RECIST 1.1 (Appendix 5). Subjects with unknown or missing response will be treated as non-responders, i.e. these subjects will be included in the denominator when calculating the percentage. The number and types of responses, as outlined in PCWG3-modified RECIST 1.1, will be listed and summarized separately, as appropriate. The observed ORR, observed confirmed and unconfirmed ORR will be reported at the interim and final analysis for each cohort specified in treated dose, if data warrant. The estimates along with 95% exact confidence interval (CI) will be provided.

Radiographic Progression-free survival (rPFS) will be defined as the time from combination study treatment start until the first date of either disease progression or death due to any cause. The date of disease progression will be defined as the earliest date of disease progression as assessed by the investigator using RECIST version 1.1 or progression on bone scan. For subjects who have not progressed or died at the time of the rPFS analysis, censoring will be performed using the date of the last adequate disease assessment. In addition, subjects with an extended loss to follow-up or who start a new anti-cancer therapy prior to a rPFS event will be censored at the date of the last adequate disease assessment (e.g. assessment where visit level response is CR, PR, or stable disease [SD]) prior to the extended loss to follow-up or start of new anti-cancer therapy, respectively. Further details on rules for censoring will be provided in the RAP. rPFS will be summarized by dose level specified in expansion cohort using Kaplan-Meier quantile estimates along with 2-sided 95% CIs

Time to PSA progression

- ***If there has been a decline from baseline*: time from start of combination treatment to <u>first</u> PSA increase that is ≥25% and ≥2 ng/mL in absolute value from the nadir, and which is confirmed by a second value 3 or more weeks later (i.e., a confirmed rising trend) at least 12 weeks after the start of treatment.**

- ***If there has NOT been a decline from baseline*: time from start of therapy to <u>first</u> PSA increase that is ≥25% and ≥2 ng/mL in absolute value from the baseline value, determined at least 12 weeks after start of treatment.**

Time to PSA progression will be summarised using Kaplan-Meier methods by dose level.

Time to radiological progression will be defined as the time from combination study treatment start until the first radiological progression by RECIST 1.1 and/ or confirmed bone progression as defined in Section 8.8.2.2. Time to radiological progression will be summarised using Kaplan-Meier methods by dose level.

Section 13.3.4.2 – Safety Analyses

Rationale for Change:

Clarification of the population used for safety analyses.

Previous text:

The All Treated Population will be used for the analysis of safety data. All serially collected safety endpoints (e.g., laboratory tests, vital signs, ECGs) will be summarized according to the scheduled, nominal visit at which they were collected and across all on-treatment time points using a "worst-case" analysis. Complete details of the safety analyses will be provided in the RAP.

Revised text:

The All Treated **Safety** Population will be used for the analysis of safety data. All serially collected safety endpoints (e.g., laboratory tests, vital signs, ECGs) will be summarized according to the scheduled, nominal visit at which they were collected and across all on-treatment time points using a "worst-case" analysis. Complete details of the safety analyses will be provided in the RAP.

Other changes to provide additional clarifications or to correct inadvertent errors in previous versions of the protocol:

Title Page:

Updated author list to include new authors: PPD and PPD and remove PPD.

Table of Contents:

Revision to Table of Contents to reflect changes to Section 3 addressed earlier in this Appendix.

List of Abbreviations:

Addition of new abbreviations to table: ORR – Objective Response Rate, PSA50 – Prostate-specific antigen decrease from baseline ≥50%, rPFS – Radiological progression free survival, and RR – Response rate

Protocol Synopsis and Section 3:

In multiple locations, revised an error in the abbreviation for PCWG2 guidelines, which was previously 2PCWG2 to PCWG2.

Section 4.1.1. – Number of Subjects:

Updated link for Section related to futility from 3.6.1 to 3.7.1.

Section 13.2.2 – Dose Expansion Phase:

Updated link for Section related to futility from 3.6.1 to 3.7.1.

Section 15 – References:

Updated date of most recent prescribing information reference for Xtandi (enzalutamide).

Appendix 9 – Protocol Amendment Changes:

For each Amendment, updated the section to provide heading numbers and dates of all protocol amendments.