pathway inhibitors). As a first step, this study will evaluate the combination of GSK525762 with new generation ADT agents, combining with either abiraterone or enzalutamide, based on the hypothesis that GSK525762, by inhibiting transcription overdrive, can overcome resistance to secondary ADT. This study will evaluate the safety and clinical activity in subjects who have progressed after treatment with abiraterone or enzalutamide, either as first line treatment (subjects treated in this study will be considered mCRPC Line 2 [L2, having failed first line treatment with or without one prior line of chemotherapy]) or on re-treatment after failure of multiple lines of therapy including prior ADT/prior chemotherapy/prior radiation therapy (subjects treated in this study will be considered mCRPC Line X [Lx]). Both populations will be included in both dose escalation and dose expansion; however, assignment during dose expansion will use forced randomization.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Co-Primary (Both Arms)	
• To determine the safety and tolerability of GSK525762, when given in combination with either abiraterone (Arm A) or enzalutamide (Arm B) in men with CRPC	• For both arms, adverse events (AEs), serious adverse events (SAEs), dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, electrocardiogram [ECG], cardiotoxicity, gastrointestinal, etc.)
• To determine clinical activity and recommended Phase 2 dose (RP2D) of GSK525762, when given in combination with either abiraterone (Arm A) or enzalutamide (Arm B) in men with mCRPC	• For both arms, primary response rate is defined as the percent of subjects achieving PSA50 at 12 weeks or thereafter (PSA50 is ≥50% decrease in Prostate Specific Antigen (PSA) from baseline)
Secondary (Both Arms)	
• To characterize the pharmacokinetics (PK) or exposure of GSK525762 and selected metabolites, when given in combination with abiraterone or enzalutamide, in men with mCRPC	• PK parameter or concentration values for GSK525762 and selected metabolites following repeat-dose oral administration in combination with abiraterone or enzalutamide
• To characterize the pharmacokinetics (PK) or exposure of abiraterone or enzalutamide, when given in combination with GSK525762, in men with mCRPC	• PK parameter or concentration values for abiraterone or enzalutamide following repeat-dose oral administration in combination with GSK525762
• To evaluate additional measures of clinical activity in subjects with CRPC	• For both arms, clinical activity evaluated by disease control rate (DCR) through 24 weeks. • Composite Response Rate (CRR) based on any of the following – a) Response based on PCWG3-modified RECIST1.1, b) PSA decrease of ≥50% at Week 12 and thereafter, or c) CTC count conversion as defined above • Objective Response Rate (ORR) defined as complete response (CR) rate plus partial response (PR) rate per Prostate Cancer

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use contraception/barrier as detailed below:

Agree to use a male condom and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year as described in Appendix 12 when having sexual intercourse with a woman of childbearing potential who is not currently pregnant. If partner becomes pregnant, agree to use/continue use of condoms until 16 weeks after the last dose of study medication.

Exclusion Criteria:

1. Surgery or local prostatic intervention (excluding a prostatic biopsy) less than 28 days of Week 1 Day 1.
2. Subjects with neuroendocrine and/or small cell CRPC
3. Recent prior therapy, defined as:
   a. Any investigational or approved non-biologic anti-cancer drug (see exception below) within 14 days prior to the first dose of GSK525762 and abiraterone/enzalutamide

   Exception: For allowed androgen deprivation therapy (hormonal, abiraterone, enzalutamide), refer to inclusion criteria. Concomitant prednisone (or equivalent) allowed in combination with abiraterone dosing.

   b. Any nitrosoureas or mitomycin C within 42 days prior to the first dose of GSK525762 and abiraterone/enzalutamide
   c. Any anti-cancer biologic agents within five half-lives prior to the first dose of GSK525762 and abiraterone/enzalutamide
   d. If the subject received radiotherapy < 90 days prior to study treatment, the irradiated lesion cannot be the only lesion used for evaluating response.

   Exception: Any radiotherapy within 14 days prior to the first dose of GSK525762 and abiraterone/enzalutamide must be limited to a single fraction of radiotherapy for the purpose of palliation (confined to one field).

   e. Any major surgery within 28 days prior to the first dose of GSK525762 and abiraterone/enzalutamide
4. Evidence of severe or uncontrolled systemic diseases (e.g., unstable or uncompensated respiratory, hepatic, renal, cardiac disease, or clinically significant bleeding episodes). Any serious and/or unstable pre-existing medical (aside from malignancy), psychiatric disorder, or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures, in the opinion of the Investigator.
   a. Systolic blood pressure higher than 150 mmHg or diastolic blood pressure higher than 90 mmHg found on 2 separate occasions separated by 1 week, despite adequate therapy, will be defined as uncontrolled hypertension.

Objectives	Endpoints
• To evaluate the effect of treatment with GSK525762 and abiraterone or enzalutamide, when given in combination, on patient-related outcomes	progression) • rPFS per PCWG3-modified RECIST 1.1 • Performance status, pain scores, quality of life
Exploratory (Both Arms)	
• To evaluate the exposure response (pharmacokinetic/pharmacodynamics [PK/PD]) relationship between GSK525762 and abiraterone or enzalutamide and safety and efficacy parameters • To characterize the pharmacodynamics of GSK525762 and abiraterone or enzalutamide, when given in combination • To evaluate the effect of treatment with GSK525762 and abiraterone or enzalutamide, when given in combination, on other measures of efficacy • To identify potential indicators of sensitivity or response to GSK525762 and abiraterone or enzalutamide, when given in combination • To describe the kinetics of tumor growth in the presence of GSK525762 for each treatment and investigate the relationship between tumor growth kinetics and clinical activity	• Exploratory analysis between exposure parameters, change from baseline levels in PD markers and safety and/or efficacy parameters. • Transcriptomic and/or protein changes in molecular markers of BET inhibition and AR signaling in tumor tissue • Overall survival (OS) over duration of study; Number of subjects with reduction in CTC of at least 30%. • Correlate baseline tumor genomic (DNA), protein and/or transcription (RNA) profiles with response. Correlate circulating biomarkers (e.g. AR-V7) with response • Tumor size or PSA levels over time, tumor growth rate constants, and time to tumor growth (TTG) predicted with the model parameters and relationship with clinical activity parameters

4. STUDY DESIGN

4.1. Overall Design

This study is a two-arm, open-label Phase Ib dose escalation and dose expansion cohort study with oral administration of GSK525762 in combination with either abiraterone (Arm A) or enzalutamide (Arm B) in male subjects with mCRPC in whom at least one line of treatment with abiraterone or enzalutamide has failed.

This study is designed to determine the maximum tolerated dose (MTD) and RP2D based on safety, tolerability, pharmacokinetic, and efficacy profiles. Arm A is designed to determine the MTD and RP2D of GSK525762 when given in combination with abiraterone, based upon safety and clinical response profiles. Arm B is designed to determine the MTD and RP2D of GSK525762 when given in combination with enzalutamide, based upon safety and clinical response profiles. During dose escalation, both treatment arms will follow a modified Toxicity Probability Interval (mTPI) design [Ji, 2013]. The design assumes (i) approximately 3 to 6 subjects per dose cohort will complete the dose-limiting toxicity (DLT) evaluation period and (ii) the true underlying

toxicity rate for GSK525762 in combination with either abiraterone or enzalutamide falls within the range from 25% to 35% and centered at 30%. Subjects included in the study must have progressed, despite previous treatment with abiraterone and/or enzalutamide (L2 or Lx). Subjects will be enrolled based upon their most recent prior treatment (e.g. subjects who were most recently treated with abiraterone will be enrolled into Arm A, and subjects most recently treated with enzalutamide will be enrolled into Arm B).

Because of the concern for potential drug-drug interactions (DDI) between GSK525762 and both abiraterone and enzalutamide, there will be extensive PK sampling as noted in Section 7.1, to specifically address the DDI effects with these drugs. Specifically, enzalutamide is a known CYP3A4 inducer, and DDI could potentially lower the exposure to GSK525762. Also, GSK525762 is a moderate CYP3A inducer and could potentially lower the exposure of abiraterone, which is a substrate of CYP3A. Therefore, emerging PK data will be used to assist with dose decisions for MTD and RP2D.

The co-primary endpoints will evaluate both safety and clinical activity of each treatment combination. The primary clinical activity outcome will be defined by the rate of ≥50% reduction in PSA (PSA50) at 12 weeks or thereafter. Secondary endpoints include: 1) DCR through 24 weeks; 2) CRR based on the following – a) response based on PCWG3-modified RECIST 1.1, b) PSA decrease of ≥50%, or c) CTC count conversion; 3) ORR defined as CR and PR rate per PCWG3-modified RECIST 1.1; 4) CTC response rate defined as percent of subjects having favorable CTC <5/7.5mL at nadir if baseline is unfavorable CTC≥5/7.5mL; 5) PSA week 4 response rate defined as percent of subjects achieving ≥30% decrease from baseline PSA after 4 weeks of study treatment; 6) time to disease progression according to PCWG3 criteria (either by PCWG3-modified RECIST 1.1 or progression in bone or PSA progression with accompanying progression by RECIST 1.1 or bone scan or clinical progression); 7) rPFS per PCWG3-modified RECIST 1.1. Other endpoints include OS, number of subjects with reduction in CTC of at least 30%, and PK will be evaluated. Safety will be evaluated by Adverse Events (AE), withdrawals due to toxicities, and changes in safety parameters from baseline (e.g., laboratory parameters, vitals, ECG).

During dose expansion, the study will employ a Bayesian predictive adaptive design that allows the trial to be monitored more frequently at multiple stages based on the utility score of the dose. Bayesian statistics will be employed to calculate the posterior probability that the utility of the dose (dU) is greater than the clinically significant minimum utility (CSMU) at interim analysis for each dose. The interim analysis will be conducted for each individual dose and it may be conducted when at least 10 evaluable subjects are available for a given dose. After the first interim analysis, the interim analysis can be conducted after every 10 additional subjects become evaluable.

For the separate interim looks in each combination in expansion cohort, the enrollment for that cohort may be stopped due to futility if the posterior probability that the utility (dU) ≥CSMU (25) is small (e.g., less than a 4% chance for the utility to be larger than the CSMU). Decisions to stop enrolment for a cohort will be based on the totality of the data, including safety/tolerability and efficacy (primary and secondary parameters).

advanced disease, both L2 and Lx subjects will be enrolled. Stratification will be utilized to target a total of 1/3 L2 and 2/3 Lx in each dose expansion cohort in both arms.

4.6. Dose Justification

4.6.1. Drug-Drug Interactions

The risk of a pharmacokinetic drug-drug interaction between GSK525762 and abiraterone is low; however, the risk of a drug-drug interaction between GSK525762 and enzalutamide is high with an anticipated significant decrease in GSK525762 exposure.

Drugs as victim: GSK525762 appears to be primarily metabolized by cytochrome P450 (CYP) 3A4 and does not appear to be metabolized by CYP2C8, CYP2C9, or CYP2C19.

Abiraterone acetate is hydrolyzed to active metabolite abiraterone, and the conversion is probably through esterase activity, and is not CYP mediated. Abiraterone is a substrate of CYP3A4. Drug-drug interaction studies using a strong CYP3A4 inducer (rifampin) reduced abiraterone exposure by 55%, suggesting avoidance of CYP3A4 inducers during abiraterone treatment. If a strong CYP3A4 inducer is warranted clinically, the dose of abiraterone should be increased to 1000 mg twice daily; once the other drug is removed, the dose of abiraterone can decrease to the labelled 1000 mg daily indication. However, co-administration of a strong CYP3A4 inhibitor (ketoconazole) didn't cause any meaningful clinical effects on the PK of abiraterone.

Enzalutamide is metabolized by CYP3A4 and CYP2C8 to an active metabolite N-desmethyl enzalutamide and primarily eliminated by hepatic metabolism. Drug-drug interaction studies using a strong CYP3A4 inducer (rifampin) reduced enzalutamide exposure by 37%, suggesting avoidance of CYP3A4 inducers during enzalutamide treatment. If a strong CYP3A4 inducer must be used, the dose of enzalutamide may be increased to 240 mg daily; if the CYP3A4 inducer is ultimately discontinued, then the dose can return to 160 mg daily.

Drugs as perpetrator: The potential for GSK525762 to inhibit the clearance of possible co-medications metabolized by major CYP enzymes was considered to be low. An *in vitro* study in human liver microsomes with clinically-relevant substrates of CYPs 2B6, 2C8 and 3A4 revealed that GSK525762 did not directly inhibit these enzymes (IC50 >100 μM), nor was there any metabolism-dependent inhibition. Based on *in vitro* and *in vivo* data showing reduction of exposure to GSK525762 following repeated administration, there is a potential for GSK525762 to be a moderate inducer of CYP3A enzymes.

Abiraterone is an inhibitor of CYP2D6 and CYP2C8, and in a drug-drug interaction trial, maximum observed concentration Cmax and Area under concentration-time curve (AUC) of dextromethorphan (a CYP2D6 substrate) were increased. These studies suggest avoidance of CYP2D6 substrates along with abiraterone; and if alternative treatment cannot be used, consider a dose reduction of the respective CYP2D6 substrate drug.

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use contraception/barrier as detailed below:

Agree to use a male condom and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year as described in Appendix 12 when having sexual intercourse with a woman of childbearing potential who is not currently pregnant. If partner becomes pregnant, agree to use/continue use of condoms until 16 weeks after the last dose of study medication.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Surgery or local prostatic intervention (excluding a prostatic biopsy) less than 28 days of Week 1 Day 1.
2. Subjects with neuroendocrine and/or small cell CRPC
3. Recent prior therapy, defined as:
   a. Any investigational or approved non-biologic anti-cancer drug (see exception below) within 14 days prior to the first dose of GSK525762 and abiraterone/enzalutamide

   Exception: For allowed androgen deprivation therapy (hormonal, abiraterone, enzalutamide), refer to inclusion criteria. Concomitant prednisone (or equivalent) allowed in combination with abiraterone dosing.

   b. Any nitrosoureas or mitomycin C within 42 days prior to the first dose of GSK525762 and abiraterone/enzalutamide
   c. Any anti-cancer biologic agents within five half-lives prior to the first dose of GSK525762 and abiraterone/enzalutamide
   d. If the subject received radiotherapy < 90 days prior to study treatment, the irradiated lesion cannot be the only lesion used for evaluating response.

   Exception: Any radiotherapy within 14 days prior to the first dose of GSK525762 and abiraterone/enzalutamide must be limited to a single fraction of radiotherapy for the purpose of palliation (confined to one field) is permitted.

   e. Any major surgery within 28 days prior to the first dose of GSK525762 and abiraterone/enzalutamide
4. Evidence of severe or uncontrolled systemic diseases (e.g., unstable or uncompensated respiratory, hepatic, renal, cardiac disease, or clinically significant bleeding episodes). Any serious and/or unstable pre-existing medical (aside from malignancy), psychiatric disorder, or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures, in the opinion of the Investigator.

- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment. All such changes will be incorporated in the protocol at the next earliest amendment.
- The IRB/Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

Procedure	SCR	Lead-In Dosing (if required)	Week 1		Week 2		Week 3		Week 4	Week 5	q4w	q8w	q12w	EOT[1, 22]
			D1	D4	D1	D4	D1	D4	D1	D1	W9 to W49	W9 to W49	W49 and thereafter	
Tumor biopsy[13]	X													
Whole blood for exploratory analyses[14]	X													
PGx blood sample[15]			X											
Biomarker Assessments														
CTC-ENU[16]	X													
CTC – ARV[17]														
Efficacy														
Computerized Tomography (CT) chest/abdomen/pelvis[18]	X													
MRI Brain[19]	X													
Bone Scan[20]	X													
EORTC-QLQ-C30, EORTC-QLQ-PR25 & BPI-SF[21]	X													

1. Applies to subjects who withdraw for any reason prior to progression or who progress during study treatment. **With the implementation of amendment 04, following the EOT visit, subjects will be no longer be contacted approximately every 3 months (± 14 days) to collect survival data.**
2. Screening echocardiogram or MUGA scans should be completed within 35 days prior to the first dose of study drugs. All other assessments should be within 28 days prior to first dose of any study drugs. Clinical labs used for screening must be within 72 hours of first does of study drugs.
3. Including dates of imaging and sizes of target lesion(s) used for RECIST 1.1 evaluation, if available.
4. Subjects will register based on most recent ADT only.
5. Complete physical examination required at screening, Week (W)1 Day (D)1 (W1D1), and end of the treatment (EOT) visits. Limited examinations permitted at all other visits, as noted. Definition of complete and limited examinations may be found in Section 7.3.1.
6. Triplicate ECG should be performed at Screening. All other timepoints may be single ECG prior to dosing and evaluated for abnormality prior to administration of dose. Triplicate ECGs would be performed as clinically indicated due to abnormal finding.
7. Refer to Table 8 for details of clinical safety labs and timing of collection
8. Scanning modality used at screening should be maintained for all subsequent scans.
9. **With the implementation of amendment 04, the PRO-CTCAE will no longer be collected.**
10. Drugs should be administered as described in Section 6.1. On PK collection days in Week 1 and Week 3, subjects should abstain from food from 8h prior until 2h after dose as described in Section 6.10.1. Dispensation of product package should occur at Day 1 visit of Week 1, Week 5 and every 4 weeks thereafter. Review of treatment compliance should occur during each study visit using a combination of staff review of subject compliance diaries and returned product packaging.

Table 9 Dose Expansion Time and Events

Procedure	SCR	Lead-In Dosing (if required)	Week 1	Week 2	Week 3	Week 4	Week 5	q4w	q8w	q12w	EOT[1, 22]
			D1	D1	D1	D1	D1	W9 to W49	W9 to W49	W49 and thereafter	
Screening[2]											
Informed Consent	X										
Demography	X										
Medical History	X										
Inclusion/Exclusion Criteria	X										
Disease Characteristics	X										
Prior Therapy[3]	X										
Register/ Randomize[4] Subject	X										
Safety											
Physical Exam[5]	X		X	X	X	X	X	X		X	X
ECOG	X		X	X	X	X	X	X		X	X
12-lead ECGs [6]	X		X	X	X	X	X	X		X	X
Clinical Laboratory Assessments[7]	X		X	X	X	X	X	X		X	X
Echocardiogram or MUGA[8]	X						X	Weeks 13, 25 and 37		X	X
PRO-CTCAE[9]	X										
AE/SAE review		Continuous from signing of informed consent									
Concomitant medication review		Continuous from signing of informed consent									
Study Treatment											
Administer GSK525762[10]			Daily								
Administer Combination product[10,11]		Daily (if required)	Daily								
Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)											
PK blood samples[12]											

Procedure	SCR	Lead-In Dosing (if required)	Week 1	Week 2	Week 3	Week 4	Week 5	q4w	q8w	q12w	EOT[1, 22]
			D1	D1	D1	D1	D1	W9 to W49	W9 to W49	W49 and thereafter	
Tumor biopsy[13]	X										
Whole blood for exploratory analyses[14]	X										
PGx blood sample[15]			X								
Biomarker Assessments											
CTC-ENU[16]	X										
CTC – ARV[17]											
Efficacy											
CT chest/abdomen/pelvis[18]	X										
MRI Brain[19]	X										
Bone Scan[20]	X										
EORTC-QLQ-C30, EORTC-QLQ-PR25 & BPI[21]	X										

1. Applies to subjects who withdraw for any reason prior to progression or who progress during study treatment. **With the implementation of amendment 04, following the EOT visit, subjects will be no longer be contacted approximately every 3 months (± 14 days) to collect survival data.**
2. Screening echocardiograms should be completed within 35 days prior to the first dose of study drugs. All other assessments should be within 28 days prior to first dose of any study drugs. Clinical labs used for screening must be within 72 hours of first does of study drugs.
3. Including dates of imaging and sizes of target lesion(s) used for RECIST 1.1 evaluation, if available.
4. Subjects will be force randomized into 1 of 2 dose cohorts in addition to the most recent ADT.
5. Complete physical examination required at screening, Week (W)1 Day (D)1 (W1D1), and end of the treatment (EOT) visits. Limited examinations permitted at all other visits, as noted. Definition of complete and limited examinations may be found in Section 7.3.1.
6. Triplicate ECG should be performed at Screening. All other timepoints may be single ECG prior to dosing and evaluated for abnormality prior to administration of dose. Triplicate ECGs should be performed as clinically indicated due to abnormal finding.
7. Refer to Table 10 for details of clinical safety labs and timing of collection
8. Scanning modality used at screening should be maintained for all subsequent scans.
9. **With the implementation of amendment 04, the PRO-CTCAE will no longer be collected.**
10. Drugs should be administered as described in Section 6.1. On PK collection days in Week 1 and Week 3, subjects should abstain from food from 8h prior until 2h after dose as described in Section 6.10.1. Dispensation of product package should occur at Day 1 visit of Week 1, Week 5 and every 4 weeks thereafter. Review of treatment compliance should occur during each study visit using a combination of staff review of subject compliance diaries and returned product packaging.
11. Lead-in administration of combination product will be dependent on treatment with applicable product prior to inclusion in the study. Abiraterone lead-in should be 7 days (Days -7 to Day 0); Enzalutamide lead-in will either be 28 days (Days -28 to Day 0) or 14 days (Days -14 to Day 0). Assigned combination product should be administered as described in

7.2. Screening and Critical Baseline Assessments

All subjects must sign written Informed Consent prior to the commencement of any study specific screening procedures. Consent may be obtained up to 28 days prior to Week 1 Day 1. Subjects will have a screening period of up to 28 days prior to Week 1 Day 1. Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of protocol-specific evaluations. In addition, disease specific assessments performed within a specified time frame prior to informed consent may be used for the study-such as biopsy specimens, prior scans (if done within 28 days) and ECHO (if done within 35 days). Subjects will acknowledge and agree to the possible use of this information for the study by giving informed consent.

A patient who is screened but not enrolled, e.g. because entry criteria were not met or enrollment did not occur within the specified time, may be considered for screening again if, for example there is a change in the patient's medical background or a modification of study entry criteria

The following procedures will be performed at the screening visit:

- Obtain written informed consent before any other study-related procedures are performed.
- Cardiovascular medical history/risk factors (as detailed in the eCRF) will be assessed at screening.
- Demographic parameters will be captured: year of birth, sex, race and ethnicity.
- Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5. Medical, surgical, and treatment history including date of first diagnosis, start and stop dates of treatment/therapy, best response to prior systemic therapy, histology, disease progression details (radiological and/or biological) as defined per PCWG3 criteria, and current sites of disease will be taken as part of the medical history and disease status. Details concerning concomitant medication will be recorded starting from screening through post-study follow-up. At a minimum, the drug name, route of administration, dose and frequency of dosing, along with start and stop dates should be recorded.

An unscheduled visit may be performed at any time during the study at the request of the patient or as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded on the eCRF as well as any other data obtained (adverse events, concomitant medications and treatments, and results from procedures or tests).

Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging studies, etc.) 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.

Investigators may be requested to perform additional safety tests during the course of the study based on newly available data to ensure appropriate safety monitoring. Appropriate

local regulatory and ethical approvals should be obtained before any additional testing is performed.

7.2.1. Critical Baseline Assessments

Baseline imaging is required for all subjects at screening, as follows:

- All subjects should have a contrast-enhanced (oral and IV) CT scan of the chest, abdomen, and pelvis performed. Baseline characterization of target- and non-target lesions should be performed as described in Appendix 5. For subjects with a contraindication to contrast-enhanced CT (e.g., documented allergy to iodinated contrast), then other modalities, such as non-enhanced CT of the chest and gadolinium-enhanced MRI of the abdomen and pelvis, may be used after discussion with the medical monitor. At each post-baseline assessment, re-evaluation of the site(s) of disease identified by these scans, using the same imaging modality, is required.
- An MRI of the brain will be required at baseline, and subjects with untreated central nervous system (CNS) disease will be excluded as described in Section 5.2.

A baseline tumor biopsy sample is required for all subjects, as follows: Archival tissue is permitted; however, if no archival tissue is available then a fresh biopsy specimen should be provided.

7.2.2. Visit Windows

With the implementation of amendment 04, specific assessments and collection of survival follow-up data will no longer be required. Please see Section 7.1 for further details.

Screening (baseline to pre-dose): Screening echocardiogram or MUGA scan should be completed within 35 days prior to first dose of study drugs. All other assessments should be completed within 28 days prior to first dose of study drugs. Screening labs collected outside of the 72-hour window prior to the first dose of study treatment must be repeated before confirming eligibility and completing first dose. Clinical labs performed during screening within 72 hours of first dose do not need to be repeated on Day 1.

Week 1: Visits for Week 1 Day 1 must be performed on the day indicated. During dose escalation, Week 1 Day 4 assessment may be ± 1 day based on subject and clinic schedule.

Week 2: Based on subject and clinic schedule, assessments can be ± 2 days.

Week 3: Assessments on Week 3 Day 1 may be delayed up to 2 days. During dose escalation, assessments on Week 3 Day 4 may be scheduled ± 2 days.

Note: The Week 3 Day 1 PK collection is timed to permit evaluation of GSK525762 PK at steady-state dosing (at least 7 consecutive days dosing prior to collection). If a subject is not receiving GSK525762 on Week 3 Day 1 as a consequence of a planned drug holiday, then serial PK collection should occur between Week 2 Day 4 and Week 2 Day

7 prior to their planned drug interruption. If subject is not receiving GSK525762 on Week 3 Day 1 due to toxicity, then serial PK collection should be rescheduled for a later time point when the subject is again being dosed for at least 7 consecutive days, and the alternate collection date noted in the eCRF. However, in this case a single pre-dose sample should still be collected to evaluate for abiraterone/enzalutamide trough concentration.

Weeks 4, 5, and 9: Clinic visits may be scheduled ± 2 days. The first disease assessment may be scheduled ± 7 days.

Every 4-week and 8-week visits after Week 9 until Week 49: After the first disease assessment has been completed, then the clinic visits can be scheduled ± 7 days. During visits with planned PK sample collection, for subjects in the alternate dosing schedule or who have interrupted dosing, the collection should be postponed until the subject has received at least 7 consecutive doses of GSK525762.

Every 12 week visits after Week 49: Visit assessments, with the exceptions to limited laboratory sampling as referenced in Section 7.1, will adjust to every 12-weeks, based on clinical judgment. Every 12-week clinic visits can be scheduled ± 7 days.

End of Treatment (EOT) visit: should be within 30 days from last dose of study drugs. If a subject is unable to return to the clinic due to hospitalization, site staffs are encouraged to telephone the subject for assessment of adverse events.

7.3. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests may be added during the course of the study based on newly available data to ensure appropriate safety monitoring. Safety data will be collected and reported from all subjects enrolled in the study (both dose escalation and expansion cohort).

7.3.1. Physical Exams

A complete physical examination will be performed by a qualified physician or designee according to local practice. Height and weight will also be measured and recorded. Height only needs to be measured once, at screening.

A complete physical examination will include measurement of vital signs (see Section 7.3.3) and assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological system, lungs, cardiovascular system, abdomen (liver and spleen), lymph nodes and extremities.

A brief physical examination will include measurement of vital signs and assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). Weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses, as well as to any prior toxicity or other event while on study. Any visible or palpable disease should be noted for response or progression as described in Appendix 5.

Table 11 Clinical Laboratory Tests

Clinical Chemistry		
Sodium	Fasting Glucose	
Potassium	Magnesium	
Chloride	Calcium (total and ionized)	
Total Carbon Dioxide	Total Protein	
Blood Urea Nitrogen[a]	Albumin	
Creatinine	Lactate dehydrogenase	
Hematology		
White blood cell count	*Automated White Blood Cell Differential:*	
Hemoglobin	Neutrophils	
Platelet count	Lymphocytes	
	Monocytes	
	Eosinophils	
	Basophils	
Liver Function		
Bilirubin (Total and Direct)[b]		
Aspartate Aminotransferase		
Alanine Aminotransferase		
Alkaline Phosphatase		
Routine Urinalysis		
Specific gravity, pH, glucose, protein, blood, and ketones by dipstick Microscopic examination (if urinalysis is abnormal, if available at participating site)		
Cardiac Studies		
Troponin (I or T at local laboratory, may be collected at central laboratory if local draw is not possible) NT-proBNP Fasting Lipid panel (Total Cholesterol, LDL, HDL, triglycerides)		
Other Studies		
Coagulation Studies:	**Endocrine Studies:**	**Safety Screening Studies:**
Prothrombin Time/INR	TSH	HIV, HbSag, HCV antibody
Partial Thromboplastin Time	Free Thyroxine 3 (Free T3)	
Fibrinogen	Free Thyroxine 4 (Free T4)	**Pancreatic Markers:**
Factor VII Assay	Hemoglobin A1c	Amylase
	PSA	Lipase
	Testosterone	

a. Direct and/or calculated BUN values are acceptable.
b. Direct bilirubin is only required if total bilirubin values are abnormal

NT-ProBNP = N-terminal pro b-type natriuretic peptide; LDL = Low-density lipoprotein; HDL = High-density lipoprotein; INR = International normalized ratio; TSH = Thyroid-stimulating hormone; PSA = Prostate-specific antigen; HIV = Human immunodeficiency virus; HbSag = Hepatitis B surface antigen; HCV = Hepatitis C virus

Note: Not all studies are performed at each visit; please refer to Section 7.1, Table 8 and Table 10 for timing of required studies

7.3.6. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 8. The severity of adverse events will be graded utilizing the NCI-CTCAE v4 [NCI-CTCAE, 2009]. Additional details regarding management of specific AEs or SAEs are described in Section 5.4, Appendix 2, and Appendix 8.

AEs will also be assessed using select items from the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Item Library (Version 1.0) for select subjects, based on the availability of translated versions.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.3.6.1. Time period and Frequency for collecting AE and SAE information

- AEs and SAEs will be collected from the signing of informed consent until the end of study visit (see Section 7.3.6.3), at the time points specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will 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 recorded and reported to GSK or designee within 24 hours, as indicated in Appendix 8.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK or designee.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 8.

7.3.6.2. Method of Detecting AEs and SAEs

Care will 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. 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?”

7.3.6.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Appendix 8 will be followed until resolution, until the condition stabilizes,

following a confirmatory disease assessment should follow the regular schedule, occurring approximately 4 weeks after the confirmatory assessment.

- To ensure comparability between the baseline and subsequent assessments, the same method of assessment and the same technique will be used when assessing response.

7.6.1. Disease Progression Endpoint

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

- Radiographic progression in by PCWG3-modified RECIST 1.1 for subjects with measurable disease
- Bone progression on bone scan according to the PCWG3 criteria (Section 7.6.3).
- PSA progression according to the PCWG3 criteria (Section 7.6.2) accompanied by any of the following: investigator-defined clinical progression or either of the above RECIST 1.1 or bone progression.

Subjects are not required to discontinue treatment on the basis of meeting PSA progression alone.

In assessing clinical activity which demonstrates a clinically meaningful primary response rate, this is defined as follows:

- A response rate of 30% at 12 weeks or later, relative to a 10% response rate suggesting no activity. This will be conducted by testing the null hypothesis that P0<=0.1 versus the alternative that P1 ≥0.3, assuming the maximum response rate for an ineffective drug is 10% and the minimum response rate for an effective drug is 30%.

These hypotheses are based on observations from a meta-analysis study in subjects who had received prior ADT both in chemo-naïve and prior chemotherapy setting. Chemo-naïve subjects treated with a second ADT (L2 subjects) had rates of ≥50% PSA decline ranging from 25.5% to 36%. Subjects treated with both prior ADT and chemotherapy (Lx subjects) had variable responses of ≥50% PSA which ranged from 4% to 26% in studies with larger subject populations (>30 subjects per study). Based on these findings, and considering a mixed population (L2 plus Lx) in both arms of the study, it is hypothesized that a response rate ≤10% would indicate no benefit for the combination of ADT failure, while a response rate of ≥30% in patients who just progressed on prior ADT will indicate there is a benefit that can be further explored [Chi, 2015].

7.6.2. PSA Response per PCWG3 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, 2016] 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 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

7.6.3. Radiographic Response per PCWG3 Criteria

Lesion assessment method and timing, evaluation of disease, disease progression and response will be conducted according to PCWG3-modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [Scher, 2016; Eisenhauer, 2009] as outlined below and in Appendix 5 of this protocol. Disease assessment modalities may include imaging (CT scan, MRI, bone scan, plain radiography) and physical examination (as indicated for palpable/superficial lesions). Contrast-enhanced CT of the chest, abdomen, and pelvis at each disease assessment timepoint is the preferred imaging modality. The same medical imaging modality with the same contrast media should be used for each time point. However, subjects with contraindication to CT may have other modalities performed as clinically indicated.

GSK requires sites to provide electronic copies (upload digital images or images on CD) of scans for all subjects for central storage which may be transferred to a central independent imaging center. This includes baseline scans and all scans performed during the course of the study. Evaluation of response and rPFS will be made by the Investigator/site radiologist. GSK may request an independent review of scans. See the SRM for additional details. With the implementation of amendment 04, transfer of scans to a central facility is no longer required.

Bone progression will be determined as the appearance of ≥2 new lesions on bone scan and at least an additional 2 bone lesions at the next scan (every 8 weeks). 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 that do not meet PCWG3 guidelines for progression.

7.6.4. Circulating Tumor Cells (CTC) per PCWG3 Criteria

Baseline CTC enumeration will be assessed. Unfavorable will be defined as ≥5/7.5mL of blood compared to favorable <5/7.5mL of blood. The number of conversations from unfavorable CTC to favorable CTC will be assessed. Absolute percent change of CTC from baseline will also be assessed.

7.7. Translational Research

After completion of the clinical trial and/or of any Interim Analysis, investigations may be performed on samples collected during the course of the trial to detect factors or profiles that correlate with response to treatment with the combination of GSK525762 and abiraterone/enzalutamide or with tumor progression status. The results gained may also be applied to medically related conditions.

Electronic CRFs (eCRF) (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

Amendment 04 applies to all global study sites. These changes are based on the decision to close out the study and stop all new enrolment as the study met protocol defined interim futility. With the implementation of amendment 04, specific assessments and collection of survival follow-up data will no longer be required. Please see Section 7.1 for further details. The study will conclude when the last subject has completed/discontinued study treatment and completed the end of treatment visit.

Any changes to the planned analyses outlined below will be covered in the Reporting and Analysis Plan (RAP).

9.1. Hypotheses

9.1.1. Dose escalation

With respect to the primary objectives and endpoints, no specific statistical hypotheses are being tested. The primary focus will be on determining the recommended dose for further exploration, based upon the safety, PK and efficacy profiles of GSK525762 plus abiraterone or enzalutamide in subjects with CRPC.

9.1.2. Dose expansion cohorts

The goal of the trial is to characterize the dose-response curve for both efficacy and safety and to identify whether there is a dose of GSK525762 with an acceptable combination of efficacy and safety.

The primary efficacy endpoint is defined as the clinically meaningful response rate (% of subjects achieving PSA reduction from baseline ≥50%) at 12 weeks and/or thereafter for the subjects treated at each dose level. The critical safety endpoint for evaluation in this trial is the percentage of subjects at dose level *d* who had dose modification due to drug related AEs. The dose modification rate R is a weighted average of the rate of different types of dose modifications: R=0.6R1+ 0.2R2+0.2R3, where R1 is the rate that subjects who withdrew from study treatment due to drug-related adverse events, R2 is the rate that subjects who had dose reductions due to drug-related adverse events, R3 is the rate that subjects who had dose interruptions due to drug-related adverse events. If a subject had more than one type of dose modifications, it will only be counted once in calculation of R and will be counted in the most severe modification category (withdrawal > reduction > interruption). A response rate of 30% or greater is desired while 10% represents a response rate that is clinically unacceptable. With respect to dose modification rate R, a dose modification rate of 12% or greater represents a dose with unacceptable tolerability.

9.4.6.2. Software Details

Simulations were conducted by the R code provided by Berry Consultants. For each assumed scenario, 1,000 sets of trials were simulated. Posterior distributions were estimated via Markov chain Monte Carlo methods using 10,000 iterations for each analysis, discarding the first 1,000 iterations for each analysis as burn-in.

9.4.6.3. Trial Sample Size and Simulation Scenarios

Sample size requirements for halting enrolment at interim analyses for simulations is based on the number of subjects enrolled; while in practice, they will be based on the number of subjects with available response data. This discrepancy is due to software feasibility, but should not have a significant impact on operating characteristics of the design. Simulations assumed the first interim analysis occurring once 10 evaluable subjects in the same cohort at the same dose level have been enrolled. An average of 5 subjects per month per cohort is assumed. The time from subject entry until the response assessment was performed is assumed to be 12 weeks. For each dose, a maximum 6 subjects will be assigned to the dose escalation stage and if that dose is safe to expand, a maximum of 30 subjects will be assigned to each cohort in total.

Although actual enrollment may vary, the estimated enrollment rate of 5 subjects per month per cohort is incorporated into the simulations. It is also assumed that a dose with DLT rate 0.1, 0.3 and 0.4 will have dose modification rate R=0.05, 0.08 and 0.12, respectively. The real enrollment rate may vary from the assumed enrollment rate in simulation, but should not impact on operating characteristics of the design. Simulation scenarios and design characteristics for one cohort on two dose levels DL1 and DL2 are listed in Table 12 under 1000 simulations. The DLT rates and RR listed are listed in the order of DL1 and DL2.

The power and type I error rate on individual dose level are calculated if the dose is determined to be lower than or equal to MTD at dose escalation stage. In the simulations that a particular dose is declared over MTD, it won't be included in the calculation. When the dose is tolerable and efficacious, the design maintains at least 80% power. The type I error rate is controlled to <0.12.

9.4.6.5. Stopping Early

Table 12 also presents the proportion of trials that halt enrolment early for futility across simulation scenarios if expansion cohort starts. Since the study requires at least 10 evaluable subjects in a particular cohort at the same dose prior to stopping early for futility, the ability for a cohort to stop early is largely dependent upon the projected maximum sample size and enrollment rate per cohort.

Non-responsive cohorts stop early for futility between 55% and 61% of the time. Responsive cohorts generally have lower than 10% chance stop early for futility.

9.4.6.6. Mean Proportion of advancing to Phase 2

To evaluate the design performance in making the decision of advancing to Phase 2, Table 12 listed the probabilities of advancing any or both of the two doses to Phase 2 after this study. In the scenario where both DLs are safe and positive, there is an 89.3% chance that at least one dose will be picked for RP2D. If the trial data indicates both doses are safe and positive, the utility function calculation discussed in Section 9.1.2 will be used as guidance to pick the best dose to take into Phase 2. When both dose levels are safe but not positive, there is 16% chance that at least one dose will be picked as RP2D.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. 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.

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

Prior to initiation of a site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

dL	Deciliter
D	Day
DAP	Data Analysis Plan
DCR	Disease Control Rate
DDI	Drug-drug interactions
DHEA	Dehydroepiandrosterone
DILI	Drug induced liver injury
DL	Dose level
DL60	Dose level 60
DL80	Dose level 80
DL100	Dose level 100
DL120	Dose level 120
DLCO	Diffusing Capacity of the Lung for Carbon Monoxide
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
dU	Utility of a given dose
E0	Baseline effect
EC50	Concentration for 50% of maximum effect
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
Emax	Maximum Effect
EORTC – QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30
EOT	End of treatment
FDA	Food and Drug Administartion
FDG	Fluorodeoxyglucose
FIH	First-in-human
g	Gram
GCP	Good Clinical Practice
GI	Gastrointestinal
GnRH	Gonadotropin-releasing hormone
GSK	GlaxoSmithKline
h, hr	hour
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HPLC	High pressure liquid chromatography
HR	Heart rate
IA	Interim analysis
IB	Investigator’s Brochure

12.5.4. Response Criteria

Evaluation of target lesions

Each site of disease should be evaluated independently. 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 5mm.
- 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 <10mm) 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

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 (28 days) after the criteria for response are first met.

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 hours** • 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 7) • If restart/rechallenge is **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, 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	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained approximately within 48h after last dose[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • 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 report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications • Record alcohol use on the liver event alcohol intake case report form **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct high pressure liquid chromatography (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, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRF forms.

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**

condition.

- 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.

12.8.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as 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 out-patient 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

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. Other situations: • 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. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.
• Refer to Appendix 6 for the required liver chemistry follow-up instructions

the scale's developer.

- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

12.8.5. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up

Objectives	Endpoints
	Working Group (PCWG3)-modified Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 • Circulating Tumor Cells (CTC) response rate defined as percent of subjects having favorable (CTC<5/7.5 mL) at nadir, if baseline is unfavorable CTC≥5/7.5mL • PSA week 4 response rate defined as percent of subjects achieving ≥30% decrease from baseline PSA after 4 weeks of study treatment • Time to disease progression according to PCWG3 criteria (either by PCWG3-modified RECIST 1.1, or progression in bone or PSA progression with accompanying progression by RECIST 1.1 or bone scan or clinical progression) • Radiological progression free survival (rPFS) per PCWG3-modified RECIST1.1
• To evaluate the effect of treatment with GSK525762 and abiraterone or enzalutamide, when given in combination, on patient-related outcomes	• Performance status, pain scores, quality of life
Exploratory (Both Arms)	
• To evaluate the exposure response (pharmacokinetic/pharmacodynamics [PK/PD]) relationship between GSK525762 and abiraterone or enzalutamide and safety and efficacy parameters	• Exploratory analysis between exposure parameters, change from baseline levels in PD markers and safety and/or efficacy parameters.
• To characterize the pharmacodynamics of GSK525762 and abiraterone or enzalutamide, when given in combination	• Transcriptomic and/or protein changes in molecular markers of BET inhibition and AR signaling in tumor tissue
• To evaluate the effect of treatment with GSK525762 and abiraterone or enzalutamide, when given in combination, on other measures of efficacy	• Overall survival (OS) over duration of study; Number of subjects with reduction in CTC of at least 30%
• To identify potential indicators of sensitivity or response to GSK525762 and abiraterone or enzalutamide, when given in combination	• Correlate baseline tumor genomic deoxyribonucleic acid (DNA), protein and/or transcription ribonucleic acid (RNA) profiles with response. Correlate circulating biomarkers (e.g. AR-V7) with response
• To describe the kinetics of tumor growth in the presence of GSK525762 for each treatment and investigate the relationship between tumor growth kinetics and clinical activity	• Tumor size or PSA levels over time, tumor growth rate constants, and time to tumor growth (TTG) predicted with the model parameters and relationship with clinical activity parameters

b. Uncontrolled diabetes mellitus (despite therapeutic; compliance to intervention) as defined by a hemoglobin A1c (HbA1c) level more than 8% and/or occurrence of more than 2 episodes of ketoacidosis in the 12 months prior to the first dose of study drug.

5. Cardiac abnormalities as evidenced by any of the following:
   a. Baseline QT duration corrected for heart rate by Fridericia's formula (QTcF) interval ≥480 msec
   b. Clinically significant conduction abnormalities or arrhythmias, such as subjects with second degree (Type II) or third degree atrio-ventricular block
   c. History or evidence of current ≥Class II congestive heart failure as defined by New York Heart Association (NYHA).
   d. History of acute coronary syndromes (including unstable angina and myocardial infarction), coronary angioplasty, or stenting within the past 3 months. Subjects with a history of stent placement requiring ongoing anti-coagulant therapy (e.g., clopidogrel, prasugrel) will not be permitted to enroll.

      NOTE: Any clinically significant ECG assessments should be reviewed by the site cardiologist prior to study entry.
   e. Known cardiac metastasis
6. Subjects with history of known bleeding disorder(s) or history of clinically significant hemorrhage (e.g., GI, neurologic), within the past 6 months.
7. Therapeutic-dose anticoagulation (e.g., warfarin, low-molecular weight heparin [LMWH], or novel oral anticoagulants) must be discontinued and coagulation parameters must be normalized prior to the first dose of GSK525762 and abiraterone/enzalutamide. Prophylactic anticoagulation, with low doses (per standard practice) of agents such as low molecular weight heparin (LMWH), direct thrombin inhibitors, or factor Xa inhibitors is permitted.
8. Concurrent use of high dose aspirin (doses up to 81 mg oral dose daily allowed, or 100 mg, as per country standards) and non-steroidal anti-inflammatory drugs (NSAIDS), except for where NSAIDs provide documented benefit over other analgesics and then to be used with caution including concomitant use of proton pump inhibitors
9. Any acute toxicities due to prior chemotherapy and / or radiotherapy that have not resolved to a National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4 grade ≤1 with the exception of chemotherapy induced alopecia and grade 2 peripheral neuropathy.
10. The patient has an active second malignancy other than curatively resected basal cell or squamous cell carcinoma of the skin, in situ carcinoma of the bladder, or other cancers for which they are treated with curative intent with no active disease in the 3 years prior to enrollment.
11. Subjects with known symptomatic brain metastasis are not suitable for enrolment. Subjects with asymptomatic, stable, treated brain metastases are eligible for study entry.

Arm A

In Arm A, eligible subjects with mCRPC will be enrolled into two dosing level cohorts to determine the MTDs (and RP2D) of GSK525762 when administered in combination with abiraterone. Eligible subjects include those that are abiraterone-refractory or resistant from second line as well as third line and above (including L2 or Lx) chemo-naive or chemo-treated), but the most recent treatment before enrolment into Arm A must be abiraterone (Figure 3).

During dose escalation, eligible subjects will be dosed in at least two dose levels to identify the two dose level cohorts to explore in dose expansion. The approved dose of abiraterone (1000 mg) will be used for all GSK525762 dose level exploration. The initial GSK525762 dose level will be dose level 60 mg (DL60), which is one dose level lower than the single-agent RP2D. If DL60 does not exceed the MTD, DL80 (GSK525762 given 80 mg QD) will be opened (Figure 3). If any dose level cohort is opened, but exceeds the maximum permitted toxicity rate, then additional subjects will not be enrolled at that dose level.

Due to emerging data (safety/tolerability/efficacy), additional dose levels may be explored. These dose levels may either be a lower daily dose level or an intermittent dose level, either at a dose level where daily treatment may be intolerable or at a lower dose. For example, if DL60 exceeds the maximum permitted toxicity rate, then an alternate/intermittent dosing at 60 mg dose level (DL60 ALT) and/or a lower daily dose level (DL-1, 40 mg) may be evaluated.

To further explore and identify the MTDs (and RP2Ds), the two most tolerable dose levels may be initiated and randomized by prior lines of therapy (L2 and Lx). A total of 30 subjects each may be enrolled into both cohorts, and approximately10 enrolled subjects will be L2 and 20 subjects will be Lx (Figure 3). If only one dose level is tolerable for dose expansion, subjects will be enrolled and not randomized. Refer to Section 4.6 for further dose information.

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. Co-administration of enzalutamide with substrates for CYP3A4 (midazolam), CYP2C9 (warfarin) and CYP2C19 (omeprazole) reduced the plasma concentration of these respective substrates. Dose adjustments for concomitant strong CYP2C8 inhibitors and CYP3A4 inducers are noted. Thus, avoid concomitant use if possible of a strong CYP2C8 inhibitor; if clinically needed, consider lowering the dose to 80 mg once daily. If that drug is subsequently discontinued, then the dose of enzalutamide can go back to 160 mg daily.

4.6.2. Starting Doses

GSK525762

A Phase I/II study (BET115521) with GSK525762 (as a single agent) was conducted in subjects with advanced solid tumors, including CRPC. Doses of 2 to 100 mg once daily and doses of 20 mg, 30 mg and 40 mg BID were evaluated. The RP2D was determined to be 80 mg QD for GSK525762. Please see Section 5.3 of the GSK525762 Investigator's Brochure [GlaxoSmithKline Document Number 2011N113741_07, 2018], which details the clinical experience to date with GSK525762 and clinical safety data in the solid tumor population up to 100 mg once daily and in the hematologic malignancy population up to 120 mg once daily.

The initial dose of GSK525762 in dose escalation administered in combination with abiraterone will be reduced to 60 mg besylate salt tablets, which represents an approximate 20% dose reduction from the single-agent RP2D.

At clinically relevant doses, enzalutamide has been shown to be an inducer of CYP3A4, with an 86% decrease in midazolam exposure. Enzalutamide also has the potential to be a clinical inducer and inhibitor of the transport protein P-glycoprotein. The initial dose of GSK525762 in dose escalation administered in combination with enzalutamide will be 80 mg besylate salt tablets. It is anticipated that enzalutamide will reduce the steady-state exposure (AUC) to GSK525762 by 60% and to GSK525762 active moiety (GSK525762 + active metabolites) by around 20% (extrapolation of the net effect in GSK525762 exposure due to CYP3A4/ P-gp Induction and P-gp Inhibition). Therefore, the initial dose of GSK525762 in both arms should be approximately equivalent.

Enzalutamide:

For enzalutamide (Xtandi), doses ranging from 30 to 600 mg have been administered to subjects with CRPC [Scher, 2010]. A dose of 160 mg has been studied extensively in Phase 3 studies and has shown superior clinical activity [Xtandi, 2015]. The currently approved dose of enzalutamide is 160 mg orally once daily. It can be given with or without food and should be taken at the same time each day. Capsules cannot be chewed, dissolved externally or opened.

As it is not anticipated that GSK525762 will impact the pharmacokinetics of enzalutamide, for the purpose of initial dosing, enzalutamide will be started at the approved dose of 160 mg once daily orally.

a. Systolic blood pressure higher than 150 mmHg or diastolic blood pressure higher than 90 mmHg found on 2 separate occasions separated by 1 week, despite adequate therapy, will be defined as uncontrolled hypertension.

b. Uncontrolled diabetes mellitus (despite therapeutic, compliance intervention) as defined by a hemoglobin A1c (HbA1c) level more than 8% and/or occurrence of more than 2 episodes of ketoacidosis in the 12 months prior to the first dose of study drug.

5. Cardiac abnormalities as evidenced by any of the following:
   a. Baseline QTcF interval ≥480 msec
   b. Clinically significant conduction abnormalities or arrhythmias, such as subjects with second degree (Type II) or third degree atrio-ventricular block
   c. History or evidence of current ≥Class II congestive heart failure as defined by New York Heart Association (NYHA).
   d. History of acute coronary syndromes (including unstable angina and myocardial infarction), coronary angioplasty, or stenting within the past 3 months. Subjects with a history of stent placement requiring ongoing anti-coagulant therapy (e.g., clopidogrel, prasugrel) will not be permitted to enroll.

      NOTE: Any clinically significant ECG assessments should be reviewed by the site cardiologist prior to study entry.
   e. Known cardiac metastasis
6. Subjects with history of known bleeding disorder(s) or history of clinically significant hemorrhage (e.g., GI, neurologic), within the past 6 months
7. Therapeutic-dose anticoagulation (e.g., warfarin, low-molecular weight heparin [LMWH], or novel oral anticoagulants) must be discontinued and coagulation parameters must be normalized prior to the first dose of GSK525762 and abiraterone/enzalutamide. Prophylactic anticoagulation, with low doses (per standard practice) of agents such as low molecular weight heparin (LMWH), direct thrombin inhibitors, or factor Xa inhibitors is permitted.
8. Concurrent use of high dose aspirin (doses up to 81 mg oral dose daily allowed or 100 mg, as per country standards) and non-steroidal anti-inflammatory drugs (NSAIDS), except for where NSAIDs provide documented benefit over other analgesics, and then to be used with caution including concomitant use of proton pump inhibitors.
9. Any acute toxicities due to prior chemotherapy and / or radiotherapy that have not resolved to a NCI-CTCAE v4 [NCI-CTCAE, 2009] grade ≤1 with the exception of chemotherapy induced alopecia and grade 2 peripheral neuropathy.
10. The patient has an active second malignancy other than curatively resected basal cell or squamous cell carcinoma of the skin, in situ carcinoma of the bladder, or other cancers for which they are treated with curative intent with no active disease in the 3 years prior to enrollment.
11. Subjects with known symptomatic brain metastasis are not suitable for enrolment. Subjects with asymptomatic, stable, treated brain metastases are eligible for study entry.

7.1. Time and Events Table

Table 7 Dose Escalation Time and Events

Procedure	SCR	Lead-In Dosing (if required)	Week 1		Week 2		Week 3		Week 4	Week 5	q4w	q8w	q12w	EOT[1, 22]
			D1	D4	D1	D4	D1	D4	D1	D1	W9 to W49	W9 to W49	W49 and thereafter	
Screening[2]														
Informed Consent	X													
Demography	X													
Medical History	X													
Inclusion/Exclusion Criteria	X													
Disease Characteristics	X													
Prior Therapy[3]	X													
Register/ Randomize[4] Subject	X													
Safety														
Physical Exam[5]	X		X		X		X		X	X	X		X	X
ECOG	X		X		X		X		X	X	X		X	X
12-lead ECGs [6]	X		X	X	X		X		X	X	X		X	X
Clinical Laboratory Assessments[7]	X		X	X	X	X	X	X	X	X	X		X	X
Echocardiogram or MUGA[8]	X									X	Weeks 13, 25 and 37		X	X
PRO-CTCAE[9]	X													
AE/SAE review		Continuous from signing of informed consent												
Concomitant medication review		Continuous from signing of informed consent												
Study Treatment														
Administer GSK525762[10]			Daily											
Administer Combination product[10,11]		Daily (if required)	Daily											
Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)														
PK blood samples[12]														

11. Lead-in administration of combination product will be dependent on treatment with applicable product prior to inclusion in the study. Abiraterone lead-in should be 7 days (Days -7 to Day 0); Enzalutamide lead-in will either be 28 days (Days -28 to Day 0) or 14 days (Days -14 to Day 0). Assigned combination product should be administered as described in Section 6.1. Please refer to combination product label for dose adjustments. Dispensation of product package should occur at Day 1 visit of Week 1, Week 5 and every 4 weeks thereafter. Review of treatment compliance should occur during each study visit using a combination of staff review of subject compliance diaries and returned product packaging.
12. **With the implementation of amendment 04, PK samples will no longer be collected.**
13. **With the implementation of amendment 04, on treatment and EOT tumor biopsies will no longer be collected.**
14. **With the implementation of amendment 04, whole blood for exploratory analyses will no longer be collected.**
15. **With the implementation of amendment 04, if a PGx sample has not yet been collected, collection will no longer be required**
16. **With the implementation of amendment 04, CTC-ENU whole blood samples will no longer be collected.**
17. **With the implementation of amendment 04, CTC-ARV whole blood samples will no longer be collected.**
18. **With the implementation of amendment 04, contrast-enhanced tomography (CT) scan data will no longer be required. Disease assessment should be managed according to local standard of care.**
19. **With the implementation of amendment 04, MRI scan data will no longer be required. Disease assessment should be managed according to local standard of care.**
20. **With the implementation of amendment 04, bone scan data will no longer be required. Disease assessment should be managed according to local standard of care.**
21. **With the implementation of amendment 04, quality of life questionnaires will no longer be collected.**
22. For subjects with progression on the basis of PSA alone may continue to receive treatment until it is determined that there is no longer clinical benefit or the subject's experiences progression by RECIST 1.1 or bone scan determination.

Section 6.1. Please refer to combination product label for dose adjustments. Dispensation of product package should occur at Day 1 visit of Week 1, Week 5 and every 4 weeks thereafter. Review of treatment compliance should occur during each study visit using a combination of staff review of subject compliance diaries and returned product packaging.

12. **With the implementation of amendment 04, PK sample will no longer be collected.**
13. **With the implementation of amendment 04, on treatment and EOT tumor biopsies will no longer be collected.**
14. **With the implementation of amendment 04, whole blood for exploratory analyses will no longer be collected.**
15. **With the implementation of amendment 04, if a PGx sample has not yet been collected, collection will no longer be required**
16. **With the implementation of amendment 04, CTC-ENU whole blood samples will no longer be collected.**
17. **With the implementation of amendment 04, CTC-ARV whole blood samples will no longer be collected.**
18. **With the implementation of amendment 04, contrast-enhanced tomography (CT) scan data will no longer be required. Disease assessment should be managed according to local standard of care.**
19. **With the implementation of amendment 04, MRI scan data will no longer be required. Disease assessment should be managed according to local standard of care.**
20. **With the implementation of amendment 04, bone scan data will no longer be required. Disease assessment should be managed according to local standard of care.**
21. **With the implementation of amendment 04, quality of life questionnaires will no longer be collected.**
22. For subjects with progression on the basis of PSA alone may continue to receive treatment until it is determined that there is no longer clinical benefit or the subject's experiences progression by RECIST 1.1 or bone scan determination.

7.3.2. ECOG Performance Status

The performance status will be assessed using the ECOG scale (Appendix 3) as specified in the Time and Events Table (Section 7.1).

7.3.3. Vital Signs

- Vital signs to be measured in semi-supine position after 5 minutes rest will include temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate.
    - In case of an abnormal first reading, three readings of blood pressure and pulse rate should be taken and averaged to give the measurement to be recorded in the eCRF.
- Vital signs will be measured more frequently if warranted by clinical condition of the subject. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.

Refer to the SRM for details regarding measurement of vital signs.

7.3.4. Cardiac Safety

7.3.4.1. Electrocardiograms

Triplicate 12-lead ECGs will be obtained at Screening. On treatment single ECGs will be completed, prior to dosing, on days specified in the Time and Events Tables during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Details will be provided in the SRM. Any values >480 msec as calculated by the machine must be confirmed manually according to Fridericia's formula. Refer to Section 5.4.2 for QTcF calculations and QTc withdrawal criteria, and to Appendix 2 for management strategies for QTcF prolongation. Triplicate ECGs should be performed as clinically indicated due to abnormal findings.

The baseline QTcF value is determined by the mean of the triplicate Screening ECG results.

ECGs should be evaluated manually on-site prior to final decision making.

ECG data will be transferred to a central facility for collection. Any central data may be reviewed by an independent central reviewer for retrospective analysis. With the implementation of amendment 04, transfer of ECG data to a central facility is no longer required.

7.3.4.2. Echocardiogram or Multigated Acquisition Scan

For all subjects, ECHO or MUGA scans will be performed at screening and at assessment times as outlined in Section 7.1. Scans should be evaluated and compared to baseline by the same reader. Copies of all scans performed on subjects who experience an absolute decrease >10% in LVEF compared to baseline concurrent with LVEF < LLN will be required by GSK for review.

until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 8.

7.3.6.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 8 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV eCRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the eCRF within one week of receipt of a CV Event data query prompting its completion.

The Death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

7.3.6.5. Other sentinel events

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, that are 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 a SAE.

7.3.6.6. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK or designee of SAEs and non-serious AEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation 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, Institutional Review Board (IRB)/Independent Ethics Committee (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.

Unless stated otherwise, these investigations may be performed irrespective of whether a response to GSK525762 and abiraterone/enzalutamide in combination is observed.

Comparative examination of pre-dosing profiles of participants may uncover known or novel candidate biomarkers/profiles which could be used to predict response to treatment with GSK525762 and abiraterone/enzalutamide in combination or provide new insights into tumor progression and medically related conditions. Comparative examination of post-dosing profiles in conjunction with pre-dosing profiles may yield known and novel candidate biomarkers/profiles and new insights which relate to the action of GSK525762 and abiraterone/enzalutamide in combination.

All samples will be retained for a maximum of 15 years after the last subject completes the trial.

Novel candidate biomarkers and subsequently discovered biomarkers of the biological response associated with tumor progression or medically related conditions and/or the action of GSK525762 and abiraterone/enzalutamide in combination may be identified by application of:

- DNA/gene, RNA and/or protein analysis of tumor tissue or circulating tumor cells (CTCs).
- Circulating cell free-DNA/RNA analysis of blood/plasma.
- Protein analysis of plasma and/or tumor tissue samples.

7.7.1. Tumor Biomarker Analysis

To further characterize the subject population, DNA, RNA and/or protein measurements may be utilized to identify predictors of sensitivity or resistance to GSK525762 and abiraterone/enzalutamide in combination utilizing baseline tissue (archival tissue or a recent biopsy) and tissue obtained at disease progression. Amplification of AR and expression of AR-variants (AR-Vs) will be retrospectively analyzed to evaluate correlation with clinical response.

7.7.2. Tumor Tissue

With the implementation of amendment 04, tumor samples will no longer be collected.

If consent is provided by the subject, an optional progression biopsy (fresh tumor tissue) for subjects who initially responded to combination therapy and then progressed is requested in order to better understand the mechanism of resistance. It is preferable to obtain the progression 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. Samples will be analyzed using appropriate technologies including, but not limited to, RNAseq, exome or targeted DNA sequencing, Immunohistochemistry (IHC), and/or quantitative reverse transcription polymerase chain reaction (qRT-PCR).

If R is lower than 12%, a withdrawal rate higher than 10% also represents a dose with unacceptable tolerability.

The response rate and dose modification rate will be jointly assessed using a utility function. For each dose expansion cohort the utility (*dU*) will be calculated and used for decision making at each interim analysis and final analysis. At the end of each arm, the dose with the highest probability of having clinically significant utility score may be picked as the RP2D. The totality of the data will be used to assess which dose will be picked as the RP2D. Further details of the calculation of utility function will be provided in RAP.

The dose expansion cohort stage of the study will employ a Bayesian predictive adaptive design that allows the trial to be monitored more frequently at multiple stages. Bayesian statistics will be employed to calculate the expected utility of the dose (dU) is greater than the clinically significant minimum utility (CSMU) at interim for each dose.

The interim analysis will be conducted for each individual dose and it may be conducted when at least 10 evaluable subjects are available for a given dose. After the first interim analysis, the interim analysis can be conducted after every 10 additional subjects become evaluable. The evaluable subjects are defined as the subjects who have had the week 12 or later PSA results or have progressed (per PSA result) or died or permanently discontinued from the study treatment.

For the separate interim looks in each combination in expansion cohort, the enrolment for that cohort may be stopped due to futility if the posterior probability that the utility (dU) >CSMU (25) is small (e.g., less than a 4% chance for the utility to be larger than the CSMU). The totality of the data including safety/tolerability and primary and secondary efficacy endpoints will be used to decide whether to stop enrolment within a cohort at an interim analysis. At the final analysis for each dose combination, the dose will be claimed positive if the posterior probability that the utility (dU) >CSMU (25) is at least 20%. However, determination of whether to pursue future development of GSK525762 plus abiraterone or enzalutamide will be based on the totality of the data including safety/tolerability, PK, PD and all efficacy endpoints.

No formal hypotheses are set up to compare the activity between the two dose levels. The difference of PSA response rate, composite response rate and DCR through 24 weeks between two dose levels within the same combination will be reported.

The maximum utility dose which is defined as the dose with the highest probability of having clinically significant utility in the same arm will be recommended as RP2D for each combination, respectively. The details of the utility function calculations will be discussed in RAP. This calculation is for guidance only, the final decision of RP2D will be based on totality of data.

Table 12 Simulation Scenarios and Design Characteristics for One cohort

Scenarios (DL1 DL2)	<= MTD (%)		Declare Efficacious and tolerable if ≤MTD (%)		Advance to phase 2 (%)			Average N		Early termination due to futility in expansion (%)	
DLT rates/ RRs	DL1	DL2	DL1	DL2	DL1	DL2	Any dose	DL1	DL2	DL1	DL2
0.1, 0.2 /0.1,0.1 Safe/Null	97.4	77.3	9.34	7.89	9.2	6.3	15.2	19.4	16.0	75.1	75.7
0.1, 0.2 /0.1,0.3 Safe/ one posi	98.1	77.6	8.46	80	8.5	62.8	70	20.5	20.4	76.45	7.35
0.1,0.2 /0.3,0.3 Safe/ Posi	98.3	79.7	85.7	80	84.6	64.7	94.6	25.8	20	5.4	7.5
0.2, 0.4 /0.1,0.3 One safe/ One Posi	89.9	38.4	11.4	78.4	11.7	36.1	44.5	16.9	6.7	64.31	5.08
0.2, 0.4 /0.3,0.3 One safe/ Posi	90.4	40.9	82.19	71.88	77.1	34.1	87.5	18	6.70	5.2	6.4
0.2, 0.4 /0.3,0.5 One safe/ Posi	90.5	38.4	83.98	95.31	77.4	44.2	90	19.6	7.0	4.75	0
0.3, 0.4 /0.3,0.3 MTD/ Posi	77.1	23	80.9	74.5	67.4	19.3	83.3	15.3	4.0	3.9	4.4

9.4.6.4. Operation Characteristics

The probability of declaring a dose is efficacious and tolerable within an individual cohort if the dose is declared lower than MTD at end of dose escalation stage (power and type I error rate) per dose are examined across scenarios for the distribution of assumed true DLT rates and RRs for each dose in the same combination arm. Similar results are expected for the other combination arm. The power is the probability declaring a tolerable and efficacious dose when the true underlying RR is larger than its corresponding historical control 0.1 and dose modification rate ≤0.12. Type 1 error rate is the probability of declaring a tolerable and efficacious dose within an individual cohort when the true underlying response rate is equal to the historical control.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors, or designee, will contact the site 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 also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.
- Source documents provide the evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.

GSK will monitor the study and site activity to verify that the:

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
L	Liter
L2	Line 2, having failed first line treatment
Lx	Failure to multiple lines of therapy including prior ADT/prior chemotherapy/prior radiation therapy
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LHRH	Luteinizing hormone-releasing hormone
LLN	Lower limit of normal
LMWH	Low molecular weight heparin
LVEF	Left ventricular ejection fraction
µM	Micromolar
mg	Milligrams
mL	Milliliter
mm	Millimeter
mmHg	Millimeter of Mercury
mmol	Millimole
msec	Milliseconds
mCRPC	Metastatic castrate-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MFD	Maximum feasible dose
m, min	Minute
MoA	Mechanism of action
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
MTD	Maximum tolerated dose
mTPI	Modified toxicity probability interval
MUGA	Multigated acquisition scan
N, n	Number
ng	Nanograms
nM	Nanomolar
NA	Not applicable
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events

remaining diameters and response determined based on percent change from baseline and percent change from nadir.

- Bone lesions with change in intensity of uptake alone do not constitute progression or regression. Pseudoprogression in the absence of symptoms or other signs of progression will be excluded.

- Bone lesion progression will require at least 2 new bone lesions on first post-treatment scan, with at least 2 additional bone lesions on the next scan. In this instance, the date of the first scan will represent the date of bone progression.

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.
- In the presence of non-measurable only disease consideration should be given to whether or not the increase in overall disease burden is comparable in magnitude to the increase that would be required to declare PD for measurable disease.
- Sites of non-target lesions, which are not assessed at a particular timepoint 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. Nodes that have progress to ≥10 mm to <15 mm are pathologic, subject to clinical discretion, and non-measurable. Previously normal lymph nodes must have grown by ≥5 mm in the short axis to be considered to have progressed.

12.6. Appendix 6: Liver Safety Required Actions and Follow up Assessments

Phase I/II 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/II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event **Subject <u>with</u> entry criteria ALT≤ 2.5 x ULN**	
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
Liver Chemistry Stopping Criteria – Liver Stopping Event **Including subjects <u>with documented</u> liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN**	
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

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)
4. 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
5. 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.

Phase I/II Oncology liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
Subject <u>with</u> entry criteria ALT≤2.5x ULN 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 <u>with documented</u> liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN** ALT ≥3x ULN and 1.5x baseline value **but** ALT <5x ULN 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 hours** 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, stabilise or return to within baseline[1] • If at any time subject meets the liver chemistry stopping criteria, proceed as described above **For subjects with entry criteria ALT≤2.5 x ULN** • 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>2.5 x ULN but ≤5 x ULN** • 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

12.8.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the eCRF 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

12.8.4. Recording of AEs and SAEs

AEs and SAE Recording:
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. • The investigator will then record all relevant information regarding an AE/SAE in the eCRF • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE eCRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms. • Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study. • Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by

information, amending the SAE data collection tool accordingly.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.8.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the SAE coordinator
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the SAE coordinator by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.