TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A phase IB open-label, dose escalation and expansion study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of GSK525762 in combination with androgen deprivation therapy and other agents in subjects with castrate resistant prostate cancer (CRPC)

Compound Number: GSK525762

Development Phase: Ib

Effective Date: 06-MAY-2020

Protocol Amendment Number: 4

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2015N238310_00	2016-OCT-13	Original
2015N238310_01	2017-FEB-01	Amendment No. 1

Amendment 1 applies to all global sites. The following changes were based on review and comments from the FDA during review:

- Clarifications to Exclusion #6 which clarified that subjects with recent clinical significant hemorrhage would be excluded from the trial
- Addition to Exclusion criteria for exclusionary medications
- Addition of Table to Section 6.3 to clarify what the dose reductions of GSK525762 should be as instructed by the study or investigator staff
- Addition of medications to both the prohibited and cautionary lists in Section 6.11.2.1 and Section 6.11.2.3
- Adjustments to Dose Adjustment/Stopping Safety Criteria in Appendix 12.2 regarding Grade 3 and Grade 4 Thrombocytopenia.

In addition to the requests of the FDA, additional changes which were included were:

- Added new information regarding monotherapy CRPC study
- Clarification to Inclusion #12 for time of use
- Update and revision to GSK525762 dose wording in Section 4.6.2
- Clarifications in when formulations of GSK525762 listed in Section 6.1 will be utilized during the trial
- Clarification to planned dose adjustment Section 6.3 to clarify impact on combination dosing during dose interruption of GSK525762
- Revision of male subject lifestyle changes, addition of Pregnancy wording with Section 7.3.7 and addition of Appendix 12 to clarify allowed contraception
- Update of the cautionary and prohibited medication tables.
- Clarification to the Time and Events table to clarify the possible lead-in dosing of either abiraterone acetate or enzalutamide, adjustment to Echocardiogram schedule and addition of EORTC-QLQ-PR25 to Dose Expansion due to erroneous absence in prior protocol
- Adjustment of Time and Events table to clarify timing of assessments post week 49 and clarification of required laboratory testing
- Addition of limited laboratory assessments every 2 week visit at Week 7 and 11
- Removal of CTC-ARV at screening, movement of the assessment of CTC-enumeration and exploratory whole blood analysis to occur in conjunction with scan assessments
- Removal of the allowance for disease assessments every 16 weeks post Week 52
- Addition of Factor VII monitoring in both dose escalation and dose expansion (at Screening, W3D1, Week 5, Week 9 and every 4 weeks thereafter and reflex testing if PT or INR are ≥1.5XULN, or in case of a bleeding event) and addition of laboratory values required prior to performing the post-dose biopsy.
- Revision of Tumor Biopsy wording to specify time required on GSK525762 prior to

on-treatment biopsy. Added platelet and coagulation requirements prior to biopsy. Revised section to also include restrictions on planned surgical procedures • Clarification of analysis populations • Addition of Appendix 13 to provide specifics for Amendment changes. • Other minor clarifications were also added		
2015N238310_02	2018-FEB-08	Amendment No. 2
Amendment 2 applies to France only due to requests from their country agency, Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) and the central Ethics Committee, Comité de Protection des Personnes (CPP) Sud-Est III. The changes from Amendment 1 include: • Revision of Inclusion Criteria #6 in Section 1 and Section 5 to clarify patient population • Addition of statement in Section 1 and Section 4.1.1 regarding the targeted number of subjects to be enrolled in France. • Clarification to Section 4.2.2.1 to require regulatory approval if above 120 mg dose of GSK525762 • Addition of statement to remove allowance of restart and/or rechallenge when liver or cardiac stopping criteria is met as per Section 5.4.1.1 and Section 5.4.2. Applicable changes also made in referenced Appendix 12.2 and Appendix 12.7. • Update to toxicity management guidelines for QTcF and liver event monitoring in Appendix 2		
2015N238310_03	2018-JUL-12	Amendment No. 3
Amendment 3 applies to all global sites. The following changes were based on review and comments from global agencies and include additions revisions noted by study team from Amendment 1: • Update to Author list, sponsor signatory, and sponsor contact list • Clarification of L2 line of therapy definition • Addition of disease control rate as secondary endpoint in multiple locations including the synopsis and Section 3, Section 4.1, Section 9.1.2., and Section 9.4.4., of the protocol • Modification of PSA progression definition in multiple locations including the synopsis and Section 3, Section 4.1, Section 7.6.1., and Section 9.4.4. of the protocol • Update to the dose futility utility wording in multiple locations to correct initial wording • Modified wording where necessary to clarify what data would be used to calculate whether a cohort would need to be closed • In multiple locations in language for both Arm A and Arm B, added or modified language to enhance flexibility for projected dose levels and/or schedules. Updated Figures of Arm A and Arm B to reflect these changes. Addition of wording to clarify that subjects would not be randomized by prior line of therapy if one dose level explored in dose expansion • Clarifications to the Inclusion/Exclusion criteria including: clarification of qualifying screening biopsy collection time period; when prior treatment could occur; removal of requirement for prior abiraterone or enzalutamide within 30 days prior to initiation of study treatment; clarification for prior chemotherapy treatment (global inclusion of		

Amendment #2 wording); revision of baseline QTcF interval per safety panel; global addition of aspirin dose per local standards; clarification of Troponin entry criteria; contraception language update; revision of seizure related criteria; and removal of prohibited medications with risk of Torsades de pointes with update to QTc language

- Revisions to various locations in Section 4.6.3 and Section 4.6.4 to update to current language in most recent Investigator's Brochure
- Modifications to QTc stopping and management wording in Section 5.4.2. and Section 12.2 to reflect updated recommendations of GSK safety panel
- Update to the definition of study completion (Section 5.5)
- Modification to description of 20 mg GSK525762 tablet and addition of 500 mg tablet of abiraterone acetate due to change in available formulation from sponsor (Section 6.1)
- Addition of language to Section 6.3. to clarify the lowest minimum allowed dose reduction in Arm B
- Removal of Section 6.3.1. for consistency with IB
- Modified Section 6.11.2.1. to clarify aspirin level and to remove prohibited medications with significant risk of Torsades de pointes and moved to cautionary section. Removed Table 7 and Table 8 and refer all readers to internet link for most current list
- Revisions to Section 7.1 including: revision of triplicate ECGs to only during Screening or abnormal findings and single ECG or other timepoints; removal of ECHO/MUGA at Week 1 Day 1; extended window for on-treatment tumor biopsy; removal of CTC-ARV testing from Week 5, 9 and End of Treatment; addition of language to footnote sections including modification of PK language (also added to Section 7.2.2.) and addition of dosing requirements for on-treatment biopsy; and addition of Week 6 sample collection per GSK safety panel recommendations
- Increase of Screening window from 14 days to 28 days, with limitation that screening laboratory results must be within 72 hours of first study treatment
- Revision to Section 7.3.4.1. regarding ECGs to ensure consistency with changes in Section 7.1 and per GSK safety panel
- Minor clarifications to Clinical Laboratory Test table
- Revision to Section 7.5.1. to ensure consistency with changes in Section 7.1 for on treatment tumor biopsy
- Removal of language in Section 7.7.3. related to planned CTC analyses
- Modification to Section 9.3.1. Analysis Populations
- For Appendix 8, Section 12.8.2, removed bullet h. as no current protocol specific SAEs for GSK525762 per IB
- Update to Appendix 12, Section 12.12.1 due to updates to the standard GSK text for contraceptive guidance and pregnancy information collection
- Other minor clarifications/revisions were included

2015N238310_04	2020-MAY-06	Amendment No. 4

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. The study will conclude when the last subject has completed/discontinued study treatment and completed the end of treatment visit.

Changes to the protocol include:

- Enrolment into the study is now closed
- Removes the requirement for specific protocol assessments and survival follow-up (Section 7.1 – Time and Events Tables)
- Update to the GSK authors, GSK signatory and GSK medical monitor

SPONSOR SIGNATORY

PPD

Hesham A. Abdullah, MD, MSc, RAC
SVP, Head of Clinical Development, Oncology

06 May 2020
Date

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Site Address
Primary Medical Monitor	PPD MD	PPD	PPD	GSK R&D, Gunnels Wood, Stevenage, Herts, SG1 2NY PPD
Secondary Medical Monitor	PPD , MD, PhD	PPD	PPD	GlaxoSmithKline 1250 South Collegeville Road, UP4410 Collegeville, PA 19426, USA PPD

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): Investigational New Drug (IND) number IND132433, EudraCT number 2016-003416-13

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 204697

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

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

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

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

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1. PROTOCOL SYNOPSIS FOR STUDY 204697

Rationale

Prostate cancer is the most frequently diagnosed cancer among men and the second-leading cause of cancer-related death in men. As the growth of prostate cancer is dependent on androgens (mediated through androgen receptor), the primary target of treatment has been focused on depleting or blocking androgen activity. While many cases of prostate cancer can be treated definitively with a multi-modal approach of surgery, radiation, and/or hormonal manipulation, metastatic prostate cancer remains an incurable disease. The next generation hormonal agents (e.g., abiraterone and enzalutamide), immunotherapy (e.g., sipuleucel-T), and novel chemotherapeutics (e.g., cabazitaxel) have increased the overall survival (OS) of patients with this disease. However, for individuals whose tumors no longer respond to hormonal manipulation (also known as metastatic castration-resistant prostate cancer [mCRPC]), current approaches are palliative.

The androgen receptor (AR) is a constitutively-expressed transcription factor in cells of the prostate, and upregulates gene expression to control cell growth, proliferation, and differentiation. The AR is activated by binding to androgens, a class of steroidal molecules that includes testosterone. Androgen-deprivation therapy (ADT) remains the cornerstone of prostate cancer therapy, even upon the emergence of resistance to primary androgen deprivation achieved by super stimulation with a gonadotrophin releasing hormone (GnRH) agonist like goserelin. In this context, direct antagonism of AR (e.g., by enzalutamide) and/or inhibition of steroid hormone synthesis (e.g., by abiraterone) has been demonstrated to provide clinical benefit upon the failure of primary ADT. Despite the success of the next-generation AR-targeted therapies, inherent or acquired resistance remains a major clinical challenge in mCRPC. Importantly, genomic analysis identified high frequency of AR pathway alterations in advanced mCRPC patients [Robinson, 2015], implicating strong dependency on AR signalling, and the continued need for alternate forms of AR inhibition.

Recent studies have shown an alternate mode of AR inhibition by targeting a new class of proteins known as bromodomain and extraterminal domains (BET). Studies have demonstrated that BET inhibition can lead to growth arrest and cell death in a variety of preclinical models, including models of CRPC. The first-in-human (FIH) study from GlaxoSmithKline (GSK), BET115521, evaluated the safety and preliminary efficacy of single-agent GSK525762, a potent inhibitor of BET proteins, in a number of tumor types including mCRPC. Preliminary data from the futility analysis of the CRPC arm indicated there were no partial or complete responses. This data will be further examined as the data continues to mature.

The study (204697) proposes to evaluate the combination of GSK525762 with other agents that have been shown to be effective in the treatment of CRPC or metastatic CRPC (mCRPC), including approved agents (e.g. abiraterone, enzalutamide etc) as well as investigational agents for mCRPC that have proven to show efficacy and can be combined based on complimentary mechanism of action (immunotherapy like anti-PD1/anti-PD-L1, poly-ADP ribose polymerase (PARP) inhibitors like oleparib/talazoparib or Phosphoinositide 3 kinase (PI3K)/Protein kinase B (AkT)

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

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

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 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 recommended Phase 2 dose (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. 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 more 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, to specifically address the DDI effects with these drugs. Specifically, enzalutamide is a known cytochrome P450 (CYP) 3A4 inducer, and DDI could potentially lower the exposure of GSK525762 levels. 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 escalation decisions, the decision for MTD and RP2D.

A comparison of primary endpoint will be performed between the investigational arms if data warrant. Efficacy data will be collected from all subjects. All evaluable subjects treated during dose escalation and in the dose expansion cohorts will be incorporated into the final analysis. The totality of data, including safety/tolerability, PK, PD, and efficacy, will be used to determine RP2D.

During dose expansion, 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 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 made to stop enrolment in any cohort will be based on the totality of the data, including safety/tolerability and efficacy.

Arm A

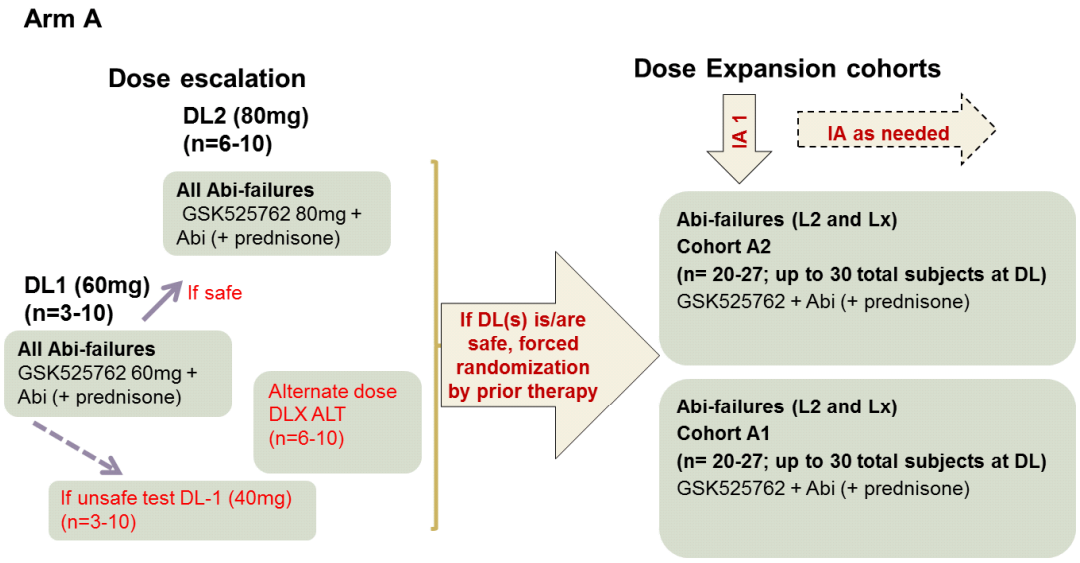
In Arm A, eligible subjects with mCRPC will be enrolled into two dosing level cohorts to determine the MTDs (and RP2D) of GSK525762 when administered in combination with abiraterone. Eligible subjects include those that are abiraterone-refractory or resistant (including L2 and Lx), but the most recent treatment before enrolment into Arm A must be abiraterone (Figure 1).

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 1). 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 schedule, 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 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 or 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 1). If only one dose level is tolerable for dose expansion, subjects will be enrolled and not randomized.

Figure 1 Study Schematic



- During dose escalation, a minimum of 3 subjects will be enrolled in first dose. A minimum of 6 subjects are required for each additional dose prior to dose expansion.
- If an Alternate dose schedule is examined in dose escalation, this dose schedule may move into dose expansion if safe and selected. Multiple alternate dose schedules may be examined. DLX = Dose to be determined based on emerging data
- IA: interim analysis to stop the arm with very low predictive probability of success on efficacy. May occur after first 10 evaluable subjects per DL. Additional IAs can occur every 10 evaluable subjects. Cohorts may be stopped at any time for futility.
- Each DL may enroll up to 30 subjects. Each DL total (up to 30) will be comprise subjects from treated during dose escalation and dose expansion. Randomization will start when more than one dose is open for enrollment.
- All Abi-failures: Includes patients that are Abiraterone refractory or resistant from second line and above (L2 or Lx)
- For Abiraterone failed subjects that are off therapy, there will be at least a 7 day lead in with abiraterone before the start of combination

Arm B

In Arm B, eligible subjects with mCRPC will be enrolled into dosing level cohorts to determine the MTDs (and RP2D) of GSK525762 when administered in combination with enzalutamide. Eligible subjects include those that are enzalutamide-refractory or resistant from second line as well as third line and above (including L2 or Lx), but the most recent treatment before enrolment into Arm B must be enzalutamide (Figure 2).

Eligible subjects will be administered escalating doses of GSK525762 in combination with the approved dose of enzalutamide (160 mg). As enzalutamide is a known CYP3A4 inducer, DDI could potentially lower the exposure of GSK525762 active moiety levels by 20%. Therefore, subjects will be enrolled at DL80 as the starting dose.

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 initial GSK525762 dose level will be dose level 80 mg (DL80), which is equivalent to one dose level lower than the single-agent RP2D due to expected DDI. If DL80 does not exceed the MTD, DL100 (GSK525762 given 100 mg QD) will be opened (Figure 2). 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.

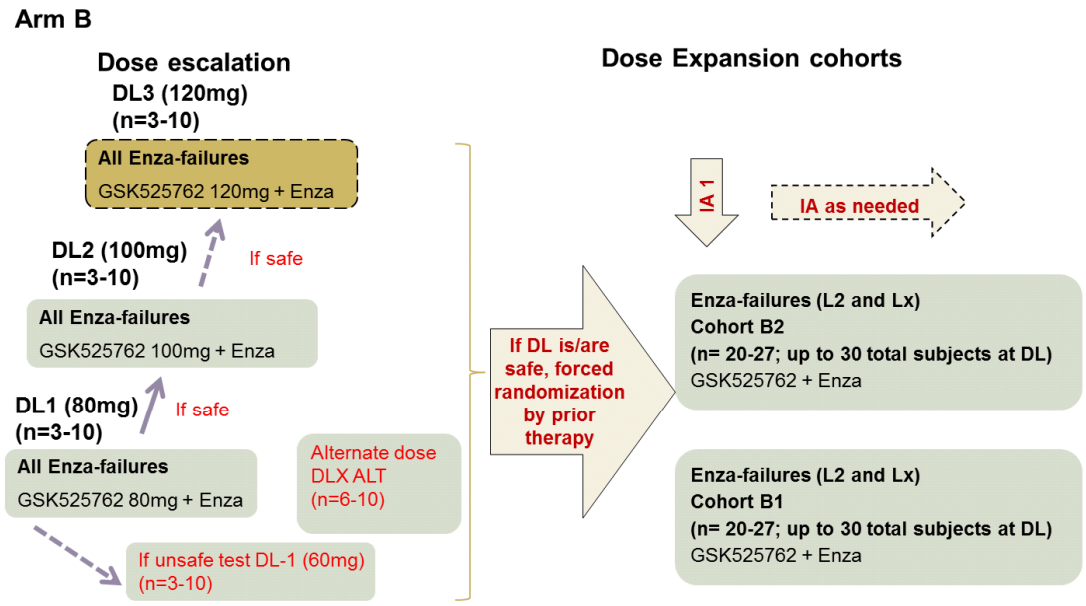
Due to emerging data (safety/tolerability/efficacy), additional dose levels may be explored. These dose levels may either be a lower daily dose level or an intermittent dose

schedule, either at a dose level where daily treatment may be intolerable or at a lower dose. For example, if DL80 exceeds the maximum permitted toxicity rate, then intermittent dosing at 80 mg dose level (DL80 ALT) and/or a lower daily dose level (DL-1, 60 mg) may be evaluated.

Based on PK analysis from DL80 and DL100 dose escalation cohorts, if the exposure to GSK525762 active moiety is 40% lower than its single agent exposure (determined from GSK525762 80 mg cohort in BET115521 study), DL120 may be opened. The study team will carefully review PK and safety data from the DL80 and DL100 levels to determine if it is acceptable to open the DL120 dose level. If DL120 is opened, subjects in DL120 will begin dosing with GSK525762 at 120 mg and the approved dose of enzalutamide.

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 or 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 2). If only one dose level is tolerable for dose expansion, subjects will be enrolled and not randomized.

Figure 2 Study Schematic



- During dose escalation, a minimum of 3 subjects will be enrolled per each opened Dose Level. A minimum of 6 subjects are required for each additional dose prior to dose expansion.
- If an Alternate dose schedule is examined in dose escalation, this dose schedule may move into dose expansion if safe and selected. Multiple alternate dose schedules may be examined. DLX = Dose to be determined based on emerging data
- IA: interim analysis to stop the arm with very low predictive probability of success on efficacy. May occur after first 10 evaluable subjects per DL. Additional IAs can occur every 10 evaluable subjects. Cohorts may be stopped at any time for futility.
- Each DL may enroll up to 30 subjects. Each DL total (up to 30) will be comprise subjects from treated during dose escalation and dose expansion. Randomization will start when more than one dose is open for enrollment.
- All Enza-failures: Includes patients that are Enzalutamide refractory or resistant from second line and above (L2 or Lx)
- For Enzalutamide failed subjects that are off therapy, there will be at least 14-28 day lead in with enzalutamide before the start of combination

Treatment Arms and Duration

All subjects will receive GSK525762 in combination with either abiraterone or enzalutamide. Subjects will begin combination therapy and continue until unacceptable toxicity, progression of disease, withdrawal of consent, death, or completion of study.

The total duration of study will depend on recruitment rates, withdrawals due to toxicity or progression or death, and, with an approximate duration of 2-3 years.

For subjects receiving GSK525762 in combination with abiraterone, daily administration of combination therapy (GSK525762 plus abiraterone) will commence immediately (Day 1) for abiraterone-failed subjects who are still on abiraterone (i.e., not stopped abiraterone dosing at progression and during screening). However, if these subjects are off abiraterone treatment for more than 3 days at the time of assignment to a cohort, there would be a lead in period for at least 7 days of abiraterone (Day -7 to Day 0) before the start of combination treatment (GSK525762 plus abiraterone on Day 1). The lead-in dosing will ensure that abiraterone is at steady state upon initiation of GSK525762 treatment.

For subjects receiving GSK525762 in combination with enzalutamide, daily administration of combination therapy (GSK525762 plus enzalutamide) will commence immediately (Day 1) for enzalutamide-failed subjects who are still on enzalutamide (i.e. not stopped enzalutamide dosing at progression and during screening). However, if these subjects are off enzalutamide treatment for more than 7 days at the time of assignment to a cohort, there would be a lead in period for at least 28 days of enzalutamide (Day -28 to Day 0) before the start of combination treatment (GSK525762 and enzalutamide). There will be a 14 day lead in period if enzalutamide (Day -14 to Day 0) interruption was less than or equal to 7 days prior to start of combination treatment (Day 1). The lead-in dosing will ensure that enzalutamide is at steady state upon initiation of GSK525762 treatment. Based upon emerging data, additional subjects may be enrolled above, at, or below the combination doses mentioned previously, in order to collect additional safety and PK data.

Initial dosing will maintain a fixed dose of abiraterone (1000 mg daily) or enzalutamide (160 mg daily). GSK525762 as a single agent was investigated at the highest dose of 80 mg (amorphous tablet)/ 75 mg (besylate tablet) once daily (Recommended Phase 2 Dose, RP2D) in the expansion cohorts of the first time in human solid tumor study (BET115521). Doses beyond the single-agent RP2D may be explored if the drug is tolerated and PK analysis demonstrates reduced GSK525762 exposure (Area under concentration-time curve [AUC] and/or maximum observed concentration [Cmax]) when administered in combination with enzalutamide. Dose reductions for individual subjects may be required, based on toxicity observed during the study, and the frequency and duration of dose reductions will be reported. If enzalutamide is discontinued for more than or equal to 7 days, then the maximum dose of GSK525762 should be the single agent RP2D of 80 mg. If enzalutamide is re-started, GSK525762 should remain at 80 mg until after at least 14 days until the dose is escalated, if applicable. Subjects who require permanent discontinuation of either abiraterone or enzalutamide in the combination may continue GSK525762 as a single agent if there is evidence of continuing benefit on treatment. If GSK525762 is continued as a single agent, the maximum dose would be 80 mg. Intra-subject dose escalations from the planned starting dose during dose escalation will not be permitted. Intra-subject dose escalation may be permitted during dose expansion if for the lower dose level only if that dose is determined to be futile.

Based on emerging information collected from PK, PD and safety/tolerability data, other dosing regimens (such as intermittent dosing for GSK525762 or staggered dosing of the two drugs) may be explored during the study.

The decision of which dose combination to identify as the RP2D from either arm will be based on the totality of data, including safety/tolerability, PK, and any preliminary efficacy data generated from the study.

The study will be considered completed for purposes of a final analysis when 70% of all the subjects enrolled have progressed or died. Survival follow-up will continue until this 70% event is met. The investigator is responsible for ensuring that consideration has been given for the post-study care of the subject's medical condition.

Type and Number of Subjects

Approximately 130 subjects worldwide may be enrolled in the study as a whole. In France, approximately 28 subjects are to be enrolled.

During dose escalation, subjects with a histologically-confirmed diagnosis of mCRPC will be treated in escalating dose level cohorts until the DL MTD(s) is/are established. The total number of subjects required will depend upon the number of escalation steps required to identify the MTD(s). Once safe DL(s) are identified, the dose expansion phase will open and subjects with a histologically-confirmed diagnosis of CRPC will be randomized based on prior lines of therapy (L2 or Lx). For both Arms, each dose level cohort may enroll or randomize up to 30 subjects. Subjects from both dose escalation and dose expansion may be combined to reach 30 subjects.

Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Written informed consent provided
2. Males ≥18 years of age (at the time written consent is obtained for screening)
3. Histologically confirmed adenocarcinoma of the prostate:
    a. Screening and on-treatment biopsy is mandatory. If adequate number of paired biopsy samples are collected (≥ 20 paired samples for each dose level in each Arm, unless an Arm is closed early), then further biopsy sampling will be considered based on available data.
    b. Screening biopsy can be waived if patient had a recent biopsy after failure of the most recent therapy (within 30 days) and the biopsy sample is secured to be sent as screening biopsy for this study.
4. Surgically or medically castrated, with testosterone levels of ≤ 50 ng/dL (<2.0 nM). If the patient is being treated with LHRH agonists/antagonists (patient who have not undergone orchiectomy) this therapy must have been initiated at least 4 weeks prior to Week 1 Day 1 and must be continued throughout the study.
5. Subjects must have failed prior therapy with abiraterone, enzalutamide, or both

a. Has completed at least 12 weeks of prior continuous therapy with abiraterone or enzalutamide in any prior line

b. Lead-in dosing period for enzalutamide only will be required under the following circumstance:

   i. If the subject has enzalutamide discontinuation for >7 days prior to dosing start with GSK525762 plus enzalutamide on trial, then an enzalutamide only lead-in dosing of 28 days is required

   ii. If the subject has enzalutamide discontinuation for ≤7 days prior to dosing start with GSK525762 plus enzalutamide on trial, then an enzalutamide only lead-in dosing of 14 days is required

   iii. If the subject is on continuous dosing with enzalutamide prior to dosing start with GSK525762 plus enzalutamide on trial, then subject can start on combined dosing at end of screening period.

c. Lead-in dosing period for abiraterone only will be required under the following circumstance:

   i. If the subject has abiraterone discontinuation for more than 3 days prior to dosing start with GSK525762 plus abiraterone on trial, then an abiraterone only lead-in dosing of 7 days is required

6. One to two line(s) of prior taxane-based chemotherapy allowed. If docetaxel chemotherapy is used more than once, this will be considered as one regimen. Subjects who have not received prior chemotherapy in any setting will qualify for study if they are ineligible for or refuse chemotherapy.

7. Documented prostate cancer progression as assessed by the investigator with one of the following:

   a. PSA progression defined by a minimum of 3 rising PSA levels with an interval of ≥1 week between each determination. The PSA value at screening must be ≥5 ug/L (5 ng/mL) if PSA is the only indication of progression; subjects on systemic glucocorticoids for control of symptoms must have documented PSA progression by PCWG3 while on systemic glucocorticoids prior to commencing Week 1 Day 1 treatment.

   b. Radiographic progression of soft tissue disease by PCWG3-modified RECIST 1.1 criteria or bone metastasis with 2 or more documented new bone lesions on a bone scan/ CT scan with or without PSA progression

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

9. Life expectancy >12 weeks

10. Able to swallow and retain orally administered medication

11. Adequate organ function as defined in Table 1.

Table 1 Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
White blood cells	>3 X 10^9/L
Absolute neutrophil count (ANC)	≥ 1.5 X 10^9/L
Hemoglobin	≥ 9 g/dL (subjects that required transfusion or growth factor need to demonstrate stable hemoglobin for 7 days of 9 g/dL)
Platelets	≥ 100 X 10^9/L
Prothrombin Time (PT)/International normalized ratio (INR) and Partial thromboplastin time (PTT)	≤ 1.5 X upper limit of normal (ULN)
Hepatic	
Albumin	≥2.5 g/dL
Total bilirubin	≤ 1.5 x ULN[a]
Aspartate transaminase (AST)	≤2.5 × ULN
Alanine transaminase (ALT)	≤2.5 × ULN OR <5x ULN is acceptable for subjects with documented liver metastases/tumor infiltration
Renal	
Creatinine OR Creatinine clearance [either directly measured or calculated by Cockcroft-Gault formula[b]]	≤1.5 X ULN the institutional upper limit of normal ≥ 50 mL/min
Cardiac	
Ejection fraction	≥ lower limit of normal (LLN) by echocardiogram or multigated acquisition scan (MUGA) and minimum of 50% LVEF
Troponin (I or T)	≤ULN
Other	
Testosterone	≤50 ng/dL

a. Isolated bilirubin >1.5 X ULN is acceptable if bilirubin is fractionated and direct bilirubin <35% or subject has a diagnosis of Gilbert's syndrome

b. Refer to Cockcroft-Gault formula

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

12. Male Participants: Contraceptive use by men or female partner should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
    Male participants are eligible to participate if they agree to the following during the intervention period and for at least 16 weeks after the last dose of study treatment:
    - Refrain from donating sperm

      PLUS either:

- 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.

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.

12. History of seizure within 6 months of first dose of study treatment or any condition that may predispose subject to seizure (e.g., prior cortical stroke or significant brain trauma) or who are currently being treated with cytochrome P450 enzyme inducing anti-epileptic drugs for seizures (use of anti-epileptic drugs to control pain is allowed in subjects not suffering from seizures unless drug is excluded due to CYP3A4 induction - phenytoin, carbamazepine, phenobarbital).
13. History of loss of consciousness or transient ischemic attack within 12 months prior to enrollment
14. Subjects with symptomatic or impending cord compression unless appropriately treated beforehand and clinically stable and asymptomatic.
15. Current use of a prohibited medication or planned use of any forbidden medications during treatment with GSK525762 and abiraterone/enzalutamide. This includes medications that are potent inducers or inhibitors of CYP3A4 enzymes or strong inhibitors of CYP2C8.
16. Subjects with gastrointestinal disorders likely to interfere with absorption of the study medication.
17. Subjects with known bleeding diathesis will be excluded from the study.
18. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases or otherwise stable chronic liver disease per investigator assessment).
19. Initiating bisphosphonate or denosumab therapy or adjusting dose/regimen within 3 months prior to Week 1 Day 1. Subjects on a stable bisphosphonate or denosumab therapy are eligible and may continue.
20. Any serious known immediate or delayed hypersensitivity reaction to GSK525762 or idiosyncrasy to drugs chemically related to the investigational drugs. Additionally, any known hypersensitivity to either enzalutamide, abiraterone or any excipients would be excluded.
21. Known history of human immunodeficiency virus (HIV)
22. Presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening.

NOTE: Subjects with positive hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative hepatitis C RNA PCR is obtained.

Analysis

The dose escalation will follow a mTPI design to identify the MTD(s) of GSK525762 in combination with either abiraterone or enzalutamide. A Bayesian adaptive design will be employed which allows the trial to be frequently monitored with the constraint of both Type I and Type II error rates. An initial interim analysis in each cohort may be performed when at least 10 evaluable subjects have been enrolled in that cohort, inclusive of subjects in both dose escalation and dose expansion. Enrolment to an individual cohort may be stopped early for toxicity or meeting futility criteria, but cohorts will not be stopped early if the response rate meets or exceeds the alternate hypothesis at the interim

analyses. Decisions to stop enrolment within a cohort will be based on the totality of the data including safety/tolerability and efficacy.

The clinical activity primary response rate will be defined as the rate of subjects achieving PSA reduction from baseline ≥50% at 12 weeks or thereafter

In assessing clinical activity which demonstrates an initial clinically meaningful 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 decrease 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.

In addition to the primary endpoint, the efficacy of each combination cohort will be evaluated based on the totality of all efficacy endpoints (primary and secondary). The following secondary efficacy endpoints will also be considered for drawing conclusions on the clinical activity of the combination(s):

- Disease control rate (DCR) at 24 weeks
- CRR based on the following – a) response based on PCWG3-modified RECIST 1.1, b) PSA decrease of ≥50% at week 12 or thereafter, or c) CTC count conversion
- ORR defined as CR and PR rate per PCWG3-modified RECIST 1.1
- CTC response rate defined as percent of subjects having favorable CTC <5/7.5mL at nadir if baseline is or conversion of unfavorable CTC≥5/7.5mL
- PSA week 4 response rate defined as percent of subjects achieving ≥30% decrease from baseline PSA at 4 weeks
- 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 PFS per PCWG3-modified RECIST 1.1

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. The study will conclude

when the last subject has completed/discontinued study treatment and completed the end of treatment visit.

2. INTRODUCTION

GSK525762 is a novel inhibitor of bromodomain and extraterminal (BET) proteins currently under investigation to treat a number of human malignancies. Enzalutamide and abiraterone are next generation androgen receptor (AR) signalling targeted therapies that have been demonstrated to provide clinical benefit upon the failure of androgen-deprivation therapy (ADT). Pre-clinically, combined inhibition of BET and AR results in improved effects on tumor cell growth compared to single agent therapy in a subset of prostate cancer models. The current protocol (study 204697) aims to test the safety, tolerability, PK, PD, and preliminary efficacy of this combination when administered concomitantly to human subjects with castrate-resistant prostate cancer (CRPC).

2.1. Study Rationale

In the United States, prostate cancer is the most common malignancy in men, affecting an estimated one out of every seven males during their lifetime [SEER, 2015]. While many cases of prostate cancer can be treated definitively with a multi-modal approach of surgery, radiation, and/or hormonal manipulation, metastatic prostate cancer remains incurable as patients with this disease become resistant to ADT as well as next generation AR-targeted therapies. Importantly, AR reactivation is one of the top resistance mechanisms in majority of these mCRPC patients, indicating the continued dependency on AR signalling. Recent studies have shown an alternate mode of AR inhibition by targeting a new class of proteins known as BET. These proteins bind to chromatin and regulate gene expression, and preclinical data suggest that combination with next generation AR-therapies may provide therapeutic benefit. The current protocol (204697) proposes to evaluate the combination of the BET inhibitor GSK525762 with second-generation AR-targeted agents such as enzalutamide or abiraterone in men with metastatic or advanced CRPC who have progressed on at least one line of prior AR-targeted therapy.

2.2. Brief Background

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

The AR is a constitutively-expressed transcription factor in cells of the prostate, and upregulates gene expression to control cell growth, proliferation, and differentiation [Ferraldeschi, 2015; Watson, 2015]. The AR is activated by binding to androgens, a class of steroidal molecules that includes testosterone. Untreated prostate cancer is dependent upon androgen at least initially for its continued growth. Most androgen production

occurs in the testes (90-95%), but the adrenal glands also produce a small fraction of circulating androgens. Thus, over the past decades, ADT remains the cornerstone of prostate cancer therapy, even upon the emergence of castration resistance to primary androgen deprivation achieved by super stimulation with a GnRH agonist like goserelin. Importantly, AR signaling axis frequently remains active despite castration therapy in CRPC, as is clinically evident by the rise in prostate-specific antigen (PSA) and hypersensitivity to even low levels of residual androgens, suggesting that continued treatment directed at the AR signaling axis may provide benefit. In this context, direct antagonism of AR (e.g., by enzalutamide) and/or inhibition of steroid hormone synthesis (e.g., by abiraterone) has been demonstrated to provide clinical benefit upon the failure of primary ADT.

Enzalutamide (Xtandi) is an orally bioavailable, AR signalling inhibitor approved in the United States (US) and the European Union for the treatment of patients with mCRPC who have previously received treatment with docetaxel, and pre-chemotherapy in the US with mCRPC [Xtandi, 2015]. Enzalutamide acts on several steps in the AR signaling pathway, including competitive inhibition of androgen binding to ARs and inhibition of AR nuclear translocation and its interaction with deoxyribonucleic acid (DNA). Abiraterone (Zytiga) is an inhibitor of cytochrome P450 (CYP) 17A1 that acts by blocking production of multiple steroid hormones, including alternative androgens that are produced in various tissues and are responsible for ADT resistance [Zytiga, 2015]. Its mechanism of action (MoA) is indirect, and does not interact directly with AR, but reduces levels of circulating androgen. This indirect MoA means that it cannot be studied in a cell culture model, but the effects in humans on androgen production results in the same effects as enzalutamide; down-regulation of AR signaling and clinical response in this AR-driven tumor type.

Despite the success of these next-generation AR-targeted therapies, inherent or acquired resistance remains a major clinical challenge in mCRPC. Importantly, integrative genomic analysis identified a potentially actionable somatic or germline event in 90% of mCRPC affected individuals, including 63% with aberrations in AR [Robinson, 2015]. The high frequency of AR pathway alterations in these advanced mCRPC patients imply the strong dependency on AR signaling, and the continued need for alternate forms of AR inhibition. In addition to AR, alterations were observed in important pathways including PI3K (49%), wingless-type MMTV integration site family member (Wnt) (18%), cell cycle (21%) and DNA repair (13%) [Robinson, 2015], suggesting the importance of combinational strategies to suppress various resistance mechanisms in mCRPC, simultaneously. There are no large clinical trials assessing the efficacy of abiraterone in patients who have previously been treated with enzalutamide and vice versa. Retrospective analyses suggest that although abiraterone has some activity in this setting, it is limited compared with patients who have not been treated with enzalutamide [Loriot, 2013; Noonan, 2013]. Conversely, enzalutamide appears to retain some activity in patients who have been previously treated with abiraterone.

Recent studies have shown an alternate mode of AR inhibition by targeting a new class of proteins known as BET [Wyce, 2013]. The BET family, comprised of bromodomain 2 (BRD), BRD3, BRD4 and BRDT, recognize acetyl groups on the tails of histones and are critical for recruiting transcriptional machinery necessary for gene expression. BRD4 has

been shown to interact with AR, and BET inhibition abrogated BRD4 localization to a subset of AR target loci and reduced AR-mediated gene transcription, causing suppression of AR signaling [Assangani, 2014]. Studies have demonstrated that BET inhibition can lead to growth arrest and cell death in a variety of preclinical models, including models of CRPC [Wyce, 2013]. The first-in-human (FIH) study from GlaxoSmithKline (GSK), BET115521, evaluated the safety and preliminary efficacy of single-agent GSK525762, a potent inhibitor of BET proteins, in a number of tumor types including mCRPC. Preliminary data from the futility analysis of the CRPC arm indicated there were no partial or complete responses. This data will be further examined as the data continues to mature. Preliminary safety and efficacy data is summarized in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2011N113741_07, 2018].
This study (204697) proposes to evaluate the combination of GSK525762 with other agents that have been shown to be effective in the treatment of CRPC or mCRPC), including approved agents (e.g. abiraterone, enzalutamide) as well as investigational agents for mCRPC that have proven to show efficacy and can be combined based on complimentary mechanism of action (immunotherapy like anti-PD1/anti-PD-L1, PARP (poly-ADP ribose polymerase) inhibitors like oleparib/talazoparib or PIK3/AkT pathway inhibitors). As a first step, this study will evaluate the combination of GSK525762 with the 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.

As described above, preclinical data suggest that BET proteins act in complex with AR at transcriptional level to mediate androgen signalling. Co-treatment with anti-androgens and BET inhibitors results in significantly improved tumor growth inhibition compared to single agent therapy in a subset of CRPC models tested (VCAP xenograft model, [Assangani, 2016]. One of the major resistance mechanisms against second generation AR-targeted therapies is the development of AR alterations including mutations and splice variants (e.g.AR-Vs). Importantly, AR-V levels were also down-regulated by another small molecule BET inhibitor JQ1 alone or in combination with enzalutamide [Chan, 2015; Assangani, 2016]. Therefore, combining BET with either abiraterone or enzalutamide gives an opportunity for vertical AR inhibition at the receptor as well as transcriptional level, offering a mechanism by which resistance may be overcome.

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.

3. OBJECTIVE(S) AND 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 castration-resistant prostate cancer (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 castration-resistant prostate cancer (CRPC)	• For both arms, primary response rate (RR)is defined as the percent of subjects achieving PSA50 at 12 weeks or thereafter (PSA50 is ≥50% decrease in 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 other measures of clinical activity in subjects with CRPC	• For both arms, clinical activity evaluated by DCR through 24 weeks • 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 • ORR defined as CR and PR rate per Prostate Cancer Working Group (PCWG3)-modified Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 • CTC response rate as defined as percent of subjects having favorable (CTC<5/7.5mL) 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

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).

Arm A

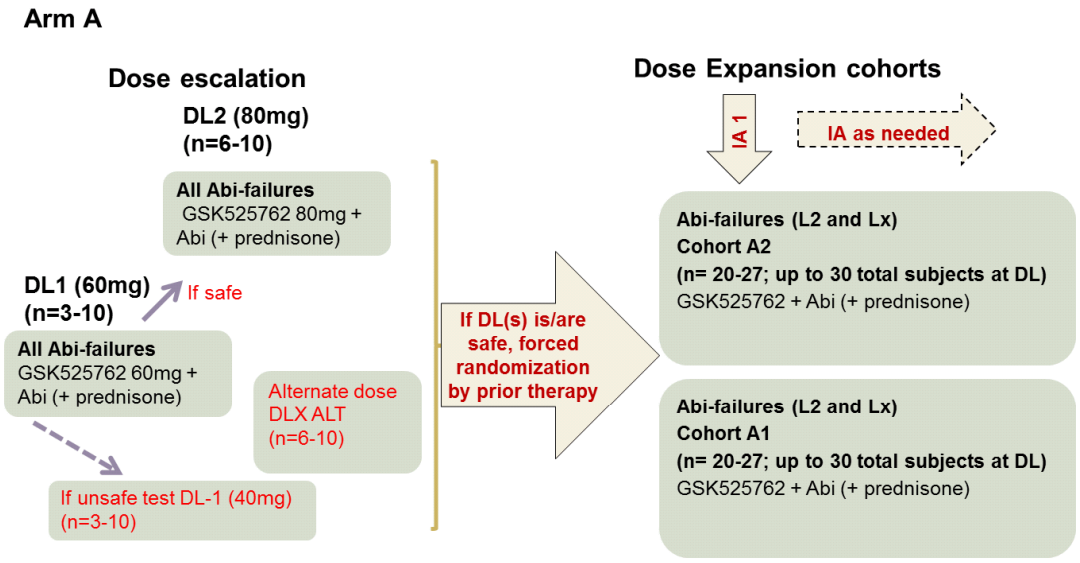
In Arm A, eligible subjects with mCRPC will be enrolled into two dosing level cohorts to determine the MTDs (and RP2D) of GSK525762 when administered in combination with abiraterone. Eligible subjects include those that are abiraterone-refractory or resistant from second line as well as third line and 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.

Figure 3 Study Schematic



- During dose escalation, a minimum of 3 subjects will be enrolled in first dose. A minimum of 6 subjects are required for each additional dose prior to dose expansion.
- If an Alternate dose schedule is examined in dose escalation, this dose schedule may move into dose expansion if safe and selected. Multiple alternate dose schedules may be examined. DLX = Dose to be determined based on emerging data
- IA: interim analysis to stop the arm with very low predictive probability of success on efficacy. May occur after first 10 evaluable subjects per DL. Additional IAs can occur every 10 evaluable subjects. Cohorts may be stopped at any time for futility.
- Each DL may enroll up to 30 subjects. Each DL total (up to 30) will be comprise subjects from treated during dose escalation and dose expansion. Randomization will start when more than one dose is open for enrollment.
- All Abi-failures: Includes patients that are Abiraterone refractory or resistant from second line and above (L2 or Lx)
- For Abiraterone failed subjects that are off therapy, there will be at least a 7 day lead in with abiraterone before the start of combination

Arm B

In Arm B, eligible subjects with mCRPC will be enrolled into dosing level cohorts to determine the MTDs (and RP2D) of GSK525762 when administered in combination with enzalutamide. Eligible subjects include those that are enzalutamide-refractory or resistant from second line as well as third line and above (including L2 or Lx), but the most recent treatment before enrolment into Arm B must be enzalutamide (Figure 4).

Eligible subjects will be administered escalating doses of GSK525762 in combination with the approved dose of enzalutamide (160 mg). As enzalutamide is a known CYP3A4 inducer, DDI could potentially lower the exposure of GSK525762 active moiety levels by 20%. Therefore, subjects will be enrolled at DL80 as the starting dose.

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 initial GSK525762 dose level will be dose level 80 mg (DL80), which is equivalent to one dose level lower than the single-agent RP2D due to expected DDI. If DL80 does not exceed the MTD, DL100 (GSK525762 given 100 mg QD) will be opened (Figure 4). 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.

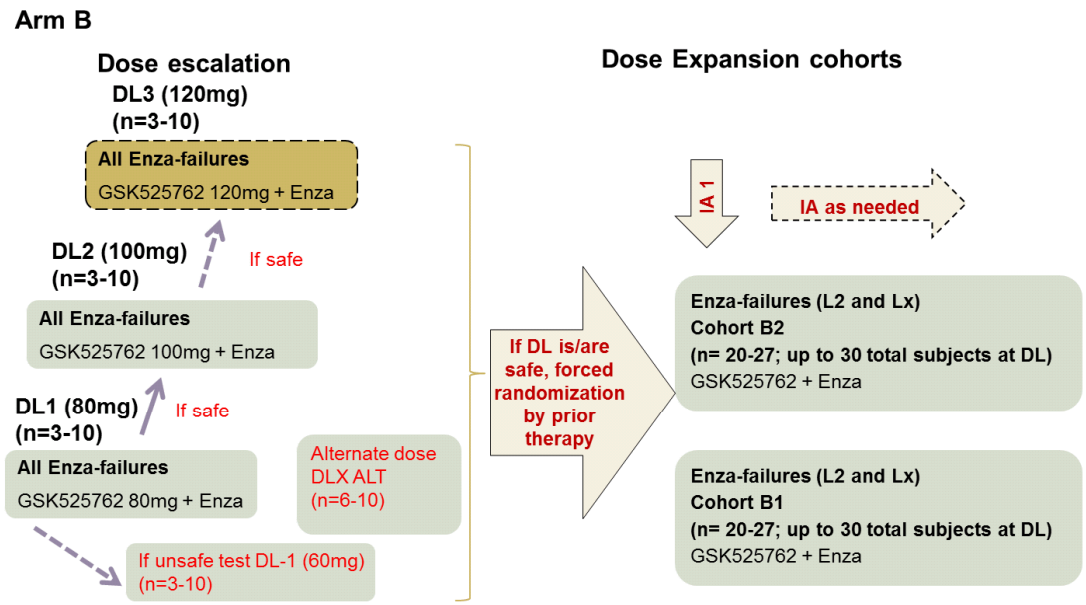
Due to emerging data (safety/tolerability/efficacy), additional dose levels may be explored. These dose levels may either be a lower daily dose level or an intermittent dose

level, either at a dose level where daily treatment may be intolerable or at a lower dose. For example, if DL80 exceeds the maximum permitted toxicity rate, then an alternate/intermittent dosing at 80 mg dose level (DL80 ALT) and/or a lower daily dose level (DL-1, 60 mg) may be evaluated.

Based on PK analysis from DL80 and DL100 dose escalation cohorts, if the exposure to GSK525762 active moiety is 40% lower than its single agent exposure (determined from GSK525762 80 mg cohort in BET115521 study), DL120 may be opened. The study team will carefully review PK and safety data from the DL80 and DL100 dose levels to determine if it is acceptable to open the DL120 dose level. If DL120 is opened, subjects in DL120 will begin dosing with GSK525762 at 120 mg and the approved dose of enzalutamide.

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 or 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 4). 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.

Figure 4 Study Schematic



- During dose escalation, a minimum of 3 subjects will be enrolled per each opened Dose Level. A minimum of 6 subjects are required for each additional dose prior to dose expansion.
- If an Alternate dose schedule is examined in dose escalation, this dose schedule may move into dose expansion if safe and selected. Multiple alternate dose schedules may be examined. DLX = Dose to be determined based on emerging data
- IA: interim analysis to stop the arm with very low predictive probability of success on efficacy. May occur after first 10 evaluable subjects per DL. Additional IAs can occur every 10 evaluable subjects. Cohorts may be stopped at any time for futility.
- Each DL may enroll up to 30 subjects. Each DL total (up to 30) will be comprise subjects from treated during dose escalation and dose expansion. Randomization will start when more than one dose is open for enrollment.
- All Enza-failures: Includes patients that are Enzalutamide refractory or resistant from second line and above (L2 or Lx)
- For Enzalutamide failed subjects that are off therapy, there will be at least 14-28 day lead in with enzalutamide before the start of combination

4.1.1. Type and Number of Subjects

Approximately 130 subjects worldwide will be enrolled in the study as a whole. In France, approximately 28 subjects are to be enrolled.

During dose escalation, subjects with a histologically-confirmed diagnosis of mCRPC will be treated in escalating dose level cohorts until the DL MTD(s) is/are established. The total number of subjects required will depend upon the number of escalation steps required to identify the MTD(s). Once safe DL(s) are identified, the dose expansion phase will open and subjects with a histologically-confirmed diagnosis of CRPC will be randomized based on prior lines of therapy (L2 or Lx). For both Arms, each dose level cohort may enroll or randomize up to 30 subjects. Subjects from both dose escalation and dose expansion may be combined to reach 30 subjects.

4.2. Dose Escalation

4.2.1. Treatments Arms and Duration

All subjects will receive GSK525762 in combination with either abiraterone or enzalutamide. Subjects will begin combination therapy and continue until unacceptable toxicity, progression of disease, withdrawal of consent, death, or completion of the study. The total duration of study will depend on recruitment rates, withdrawals due to toxicity or progression or death, and, with an approximate duration of 2 to 3years.

This study will consist of dose escalation and dose expansion cohorts. A mTPI design will be followed during dose escalation to establish safe DLs to move to dose expansion. During dose expansion, subjects who have failed prior abiraterone/enzalutamide-treatment both as L2 as well as Lx will be enrolled to either of the following arms:

- Forced randomization of subjects that are abiraterone-refractory or resistant from L2 and Lx to the two most tolerable dose level cohorts with 1/3 of the subjects from L2 and 2/3 of the subjects from Lx: - GSK525762 + abiraterone/prednisone (Arm A).
- Forced randomization of subjects that are enzalutamide-refractory or resistant from L2 and Lx to the two most tolerable dose level cohorts with 1/3 of the subjects from L2 and 2/3 of the subjects from Lx:- GSK525762 at RP2D+ enzalutamide (Arm B)

For subjects receiving GSK525762 in combination with abiraterone, daily administration of combination therapy (GSK525762 and abiraterone) will commence immediately (Day 1) for abiraterone-failed subjects who are still on abiraterone (i.e, not stopped abiraterone dosing at progression and during screening). However, if these subjects are off abiraterone treatment for more than 3 days at time of assignment to a cohort, there would be a lead in period for at least 7 days of abiraterone (Day -7 to Day 0) before the start of combination treatment (GSK525762 and abiraterone). The lead-in dosing will ensure that abiraterone is at steady state upon initiation of GSK525762 treatment (Table 2). Based on emerging information collected from PK, PD and safety/tolerability data, other dosing regimens (such as BID dosing for both drugs or intermittent dosing for GSK525762 or staggered dosing of the two drugs) may be explored during the study.

Table 2 Prior Abiraterone Treatment Guidance

Situation:	Action:
Subject has continued prior abiraterone dosing at time of assignment	Subject may start combination treatment once assigned to cohort.
Subject has stopped abiraterone for more than 3 days at time of assignment	Subject must initiate lead-in single agent abiraterone dosing for at least 7 days prior to initiation of combination treatment with GSK525762

For subjects receiving GSK525762 in combination with enzalutamide, daily administration of combination therapy (GSK525762 plus enzalutamide) will commence immediately (Day 1) for enzalutamide-failed subjects who are still on enzalutamide (i.e. not stopped enzalutamide dosing at progression and during screening). However, if these subjects are off enzalutamide treatment for more than 7 days at the time of assignment to a cohort, there would be a lead in period for at least 28 days of enzalutamide (Day -28 to Day 0) before the start of combination treatment (GSK525762 and enzalutamide). There will be a 14 day lead in period (Day -14 to Day 0) if enzalutamide interruption was less than or equal to 7 days prior to start of combination treatment (Day 1). The lead-in dosing will ensure that enzalutamide is at steady state upon initiation of GSK525762 treatment (Table 3). Based upon emerging data, additional subjects may be enrolled above, at, or below the combination doses, in order to collect additional safety and PK data.

Table 3 Prior Enzalutamide Treatment Guidance

Situation:	Action:
Subject has continued prior enzalutamide dosing at time of assignment	Subject may start combination treatment once assigned to cohort.
Subject has stopped enzalutamide for more than 7 days at time of assignment	Subject must initiate lead-in single agent enzalutamide dosing for at least 28 days prior to initiation of combination treatment with GSK525762
Subject has stopped enzalutamide for 7 or less days at time of assignment	Subject must initiate lead-in single agent enzalutamide dosing for at least 14 days prior to initiation of combination treatment with GSK525762

4.2.2. Dose Escalation

4.2.2.1. Planned Dose Levels

GSK525762 as a single agent was investigated at the highest dose of 80 mg (amorphous tablet)/ 75 mg (besylate tablet) once daily (Recommended Phase 2 Dose, RP2D) in the expansion cohorts of the first time in human solid tumor study (BET115521). All doses of GSK525762 refer to the besylate tablet formulation. For Arm A, projected dose levels

of GSK525762 are 60 mg and 80 mg administered once daily. 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.

For Arm B, projected dose levels of GSK525762 are 80 mg, and 100 mg administered once daily. A dose of 120 mg may be evaluated in combination with enzalutamide based on emerging PK and safety data. 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 DL80 exceeds the maximum permitted toxicity rate, then an alternate/intermittent dosing at 80 mg dose level (DL80 ALT) and/or a lower daily dose level (DL-1, 60 mg) may be evaluated.

Projected dose levels of abiraterone and enzalutamide are 1000 mg and 160 mg respectively, administered once daily. No doses will be explored beyond 1000 mg abiraterone or 160 mg enzalutamide, these doses that are considered to be the Maximum Feasible Dose (MFD), unless emerging PK data demonstrate reduced exposure of either drug in combination compared to single agent. As determined from pre-clinical studies, the maximum clinical dose of GSK525762 will not exceed 200 mg. Any GSK525762 dose above 120 mg would require regulatory authority review and approval.

4.2.2.2. Dose-Limiting Toxicity

An event will be considered a DLT if it occurs within the first 28 days of combination treatment (Day 1 to Day 28) and meets one of the criteria listed in Table 4, unless it can be clearly established that the event is unrelated to treatment.

Table 4 Dose-Limiting Toxicity Criteria

Toxicity	DLT Definition
Hematologic	• Grade 3 or greater neutropenia for ≥5 days • Febrile neutropenia • Grade 4 anemia of any duration • Grade 4 thrombocytopenia of any duration or Grade 3 thrombocytopenia with bleeding
Non-hematologic	• ALT >3x upper limit of normal (ULN) + bilirubin ≥2xULN (>35% direct) or ALT between 3-5 X ULN with bilirubin < 2xULN but with hepatitis symptoms or rash (See Section 5.4.1 for Liver Stopping Criteria) • Grade 3 nausea, vomiting or diarrhea that does not improve within 72h despite appropriate supportive treatment(s) • Grade 4 nausea, vomiting, or diarrhea • Grade 3 hypertension[a] (uncontrolled despite addition of up to 2 antihypertensive medications) • Grade 4 hypertension • Grade 3 or greater clinically significant non-hematologic toxicity (including QT duration corrected for heart rate by Fridericia's formula (QTcF) except toxicities listed in Section 4.2.2.3. • Ejection fraction < lower limit of normal (LLN) with an absolute decrease of >10%from baseline
Other	• Inability to receive at least 75% of scheduled doses in the DLT observation period due to drug-related toxicity, or any toxicity which requires permanent discontinuation of investigational agent(s) during the DLT observation period[b] • Grade 2 or higher toxicity that occurs beyond 28 days which in the judgment of the investigator and Medical Monitor is considered to be a DLT

Toxicity Grading based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4 [NCI-CTCAE, 2009]

a. Grade 3 hypertension adequately controlled by antihypertensive medication(s) is not considered to be a DLT.
b. Subjects unable to receive at least 75% of scheduled doses for reasons other than toxicity (e.g., acute illness, disease progression) will not be evaluable for DLT purposes and will be replaced in the cohort.

Refer to Appendix 2 for management of selected toxicities.

4.2.2.3. Non-Limiting Toxicities

The following toxicities have been deemed to be non-serious for the purposes of this study. These toxicities will not be taken into account for dose escalation decisions unless, in the opinion of the investigator and the Medical Monitor, they represent a dose-limiting toxicity. For all other toxicities and their management, see Appendix 2.

- Grade 2 or less:
  - Fatigue
  - Rash
  - Alopecia

- Grade 3 or less nausea, vomiting, or diarrhea that improves to ≤Grade 1 within 24h (refer to Section 6.11.2.3 for discussion of permitted anti-emetic regimens)
- Electrolyte imbalance or other laboratory abnormalities that improves to ≤ Grade 1, without clinical sequelae, within 24h

4.2.2.4. Maximum Dose Increment

The pre-planned dose levels are described in Section 4.2. Only GSK525762 will be dose-escalated at each dose escalation step.

4.2.2.5. Dose Escalation Decisions

A data review team, consisting (at a minimum) of the investigator(s), medical monitor(s), safety physician, pharmacokineticist, clinical representatives, and statistician, will be responsible for determining whether dose escalation should continue as planned according to the mTPI design rules (Figure 5) [Ji, 2013]. Prior to the dose escalation decision, the data review team will review available relevant data on all adverse events including non-DLT toxicities, laboratory assessments and other safety evaluations, as well as PK data. The dose decision and rationale for each cohort will be documented in writing with copies maintained at each study site and in the master study files at GlaxoSmithKline (GSK).

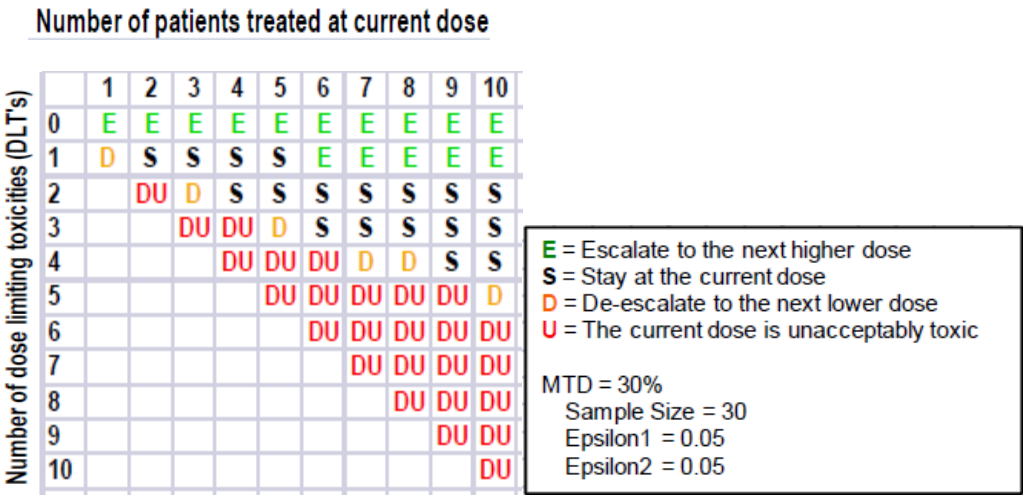
Dose escalation will follow mTPI dose-escalation procedure. The design assumes (i) approximately 3 to 6 subjects per dose cohort will complete the dose-limiting toxicity (DLT) evaluation period and (ii) the true underlying toxicity rate for GSK525762 in combination with enzalutamide falls within the range from 25% to 35% and centered at 30%. Dose limiting toxicities (DLTs) are based on any observed toxicity in the first 28 days of treatment (please see Section 4.2.2.2). At DL60, 3 subjects will be enrolled. If no DLT is observed, proceed to next dose level. If one of the three evaluable subject experiences a DLT, then 3 additional subjects will be enrolled at that dose level. Evaluation of available safety data from at least 6 subjects who have completed a minimum of 28 days (1 cycle) at the current highest safe dose level is required prior to expanding a cohort.

A modified Toxicity Probability Interval (mTPI) design will be implemented (Figure 5) [Ji, 2013]. The mTPI decision rule will be followed for monitoring safety until up to 10 subjects have been assigned at the same dose.

The design assumes (i) Approximately 3-6 subjects will complete the DLT evaluation period and (ii) the true underlying toxicity rate for GSK525762 in combination with abiraterone or enzalutamide falls within the range from 25% to 35% and centered at 30%. The monitoring rules guiding dose escalation are provided in Figure 5. Columns provide the numbers of subjects treated at the current dose level, and rows provide the corresponding numbers of subjects experiencing toxicity. The entries of the table are dose-finding decisions (i.e., E, S, and D) representing escalating the dose, staying at the same dose, and de-escalating the dose. If the current dose is at the highest dose level and the decision is E, it indicates that the highest dose level is below MTD and the next subject(s) will be treated at the same dose level. In addition, decision U means that the

current dose level is unacceptable because of high toxicity and should be excluded from the trial. For example, when one of three subjects experiences toxicity, the decision can be located at row 1 and column 3, which is S – to stay at the current dose level. Consequently the next cohort of subjects will be treated at the same dose level currently being used. If zero of three subjects experiences toxicity, the decision is at row 0 and column 3, which is E – to escalate if there is higher available dose otherwise stop dose escalation if there are 6 evaluable subjects on the current dose. Thus, the next cohort of subjects will be treated at the next-higher dose level. If three of three subjects experiences toxicity, the decision is DU – to de-escalate to the next-lower dose level and exclude the current dose from the trial, because the high toxicity level is unacceptable.

Figure 5 Dose-finding spreadsheet of the modified toxicity probability interval (mTPI) method



	1	2	3	4	5	6	7	8	9	10
0	E	E	E	E	E	E	E	E	E	E
1	D	S	S	S	S	E	E	E	E	E
2		DU	D	S	S	S	S	S	S	S
3			DU	DU	D	S	S	S	S	S
4				DU	DU	DU	D	D	S	S
5					DU	DU	DU	DU	DU	D
6						DU	DU	DU	DU	DU
7							DU	DU	DU	DU
8								DU	DU	DU
9									DU	DU
10										DU

The spreadsheet was generated based on a beta/binomial model and precalculated before trial initiation. The letters in different colors are computed based on the decision rules under the mTPI method and represent different dose-finding actions. In addition to actions de-escalate the dose (D), stay at the same dose (S), and escalate the dose (E), the table includes action unacceptable toxicity (U), which is defined as the execution of the dose-exclusion rule in mTPI.

The cohort may be expanded up to 10 subjects to further evaluate safety, pharmacokinetics and tolerability before dose escalation or reduction decision is determined.

4.2.2.6. Alternative Dosing Schedules

Alterations may be made to the schedule of administration and/or PK/PD sampling schedule based on the results of emerging PK, PD, and safety data.

Schedules that incorporate a recovery period may be explored (e.g., 2 weeks on, 1 week off). This approach will be considered if the safety and PK data suggest that a therapeutic exposure cannot be achieved using the initial schedule without excessive toxicity. The starting dose for the alternate schedule will be no higher than the maximum tolerated or completed dose level with the initial schedule. Escalation can then proceed as described in Section 4.2.2.

The dosing schedule may also be adjusted to expand a prior dose cohort to further evaluate safety, pharmacokinetic and/or pharmacodynamic findings at a given dose level, or to add cohorts to evaluate additional dose levels. The study procedures for these additional subject(s) or cohort(s) will be the same as that described for other study subjects.

Any changes to the dosing schedule may be made only after review of all available data and clearance by the medical monitor(s). Any planned changes will apply to a cohort of subjects and not an individual subject. Changes will be communicated to the site in writing along with justification and data supporting the change. A modified Study Reference Manual (SRM), including updated Time & Events Table, will be provided to the sites prior to initiation of the alternative regimen.

4.3. Decision to Proceed to Expansion phase

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.

Dose escalation will be considered complete when a MTD have been determined, any remaining subjects have completed the 28-day DLT observation period and have undergone all necessary sample collection procedures scheduled for the first four weeks on therapy (e.g., the on-dose tumor biopsy and any associated blood draws). At that time, all available data (including data from subjects who prematurely discontinue therapy) will be compiled and summarized. The totality of the data, including safety/tolerability, PK, PD, and efficacy will be used to determine expansion cohort dose for GSK525762 to be administered in combination. Clinical activity data from evaluable subjects treated at or above the dose combination selected as the RP2D will be considered in the analysis of efficacy described in Section 9.4.4.

At the completion of dose escalation, any subjects still receiving therapy with GSK525762 and/or abiraterone/enzalutamide may continue receiving drug(s) until progression, death, withdrawal of consent, unacceptable toxicity, or completion of study as described in Section 5.4. Clinic visits and efficacy analysis should continue as described in the Time and Events Table.

4.4. Expansion Cohorts

4.4.1. Type and Number of Subjects

All subjects with a histologically-confirmed diagnosis of CRPC will be enrolled. 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). The total number of subjects required will depend upon the number of escalation steps required to identify the MTD(s). Once safe DL(s) are identified, the dose expansion phase will open and subjects

with a histologically-confirmed diagnosis of CRPC will be randomized based on prior lines of therapy (L2 or Lx). For both Arms, each dose level cohort may enroll or randomize up to 30 subjects. Subjects from both dose escalation and dose expansion may be combined to reach 30 subjects. If only one DL is opened for dose expansion, subjects will continue to be enrolled and their prior line of therapy (L2 or Lx) will be collected, but subjects will not be randomized.

Refer to Section 9.1.1 for the statistical rationale for the number of subjects to be enrolled.

During dose expansion, subjects will not be replaced if they prematurely discontinue therapy.

4.4.2. Dose Selection

For both Arms, it is anticipated that the two most tolerable dose level combinations per arm will be carried forward into expansion cohorts. If data warrants, only one dose level combination may be carried into dose expansion.

4.4.3. Statistical Design

During dose expansion, each combination cohort will employ a Bayesian adaptive design that allows the trial to be frequently monitored with the constraint of both Type I and Type II error rates. This design allows the enrollment to be halted due to futility. For details of the design and decision rules, refer to Section 9.1.2.

Inference stemming from the Bayesian probabilities of efficacy and tolerability in subjects harboring mCRPC are intended to inform decision making. Actual decisions will depend on the totality of the efficacy and safety data. The decision to terminate a cohort will not depend solely on the results of the statistical model but will take all factors into account, including the results of the model, additional efficacy parameters, safety, tolerability, PK, and PD data. In some cases, the enrolment for a cohort won't stop even if the model suggests a low likelihood of clinically meaningful utility score in that combination.

4.5. Design Justification

Dose escalation will establish whether the combination of GSK525762 and abiraterone/enzalutamide are safe in targeted dose levels for abiraterone or targeted dose levels for enzalutamide. For each arm, up to 2 dose levels will be taken forward, with a lower and higher GSK525762 dose, either as a continuous or intermittent dose administration. Further evaluation will be conducted by the study team to determine if only 1 dose level will be required per either Arm during dose expansion.

By taking forward up to two doses per arm into dose expansion, the study may be able to determine the ideal dose level in combination with abiraterone/enzalutamide that can be defined as the RP2D for each combination. To further establish a potential signal in

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.

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.

This same dose will also be used during the lead in period for subjects who have discontinued enzalutamide prior to coming onto this study.

Abiraterone:

For Abiraterone (Zytiga), doses ranging from 250 to 2000 mg have been administered to subjects with CRPC [Attard, 2008]. A dose of 1000 mg has been studied extensively in Phase 3 studies and has shown superior clinical activity [Zytiga, 2015]. The currently approved dose of abiraterone is 1000 mg orally once daily. Additionally, as per abiraterone label, 5 mg twice daily prednisone must be administered. Administration of Abiraterone orally is done in a fasted state with the prescribing information suggesting no food 2 hours prior to and for at least 1 hour after abiraterone dosing. Tablets must be swallowed with water and cannot be crushed or chewed.

As it is not anticipated that GSK525762 will have a major impact on the pharmacokinetics of abiraterone, for the purpose of initial dosing in the Phase 1 portion, abiraterone will be started at the approved dose of 1000 mg once daily orally in fasted conditions with co-administration of prednisone.

4.6.3. Overlapping Toxicities

As monotherapy, GSK525762 and enzalutamide/abiraterone have overlapping toxicity profiles, including effects on the hepatic, hematopoietic, gastrointestinal, and reproductive systems. The potential for additive severity and incidence of these adverse events exists.

Due to the anticipated reductive effect that enzalutamide is expected to have on GSK525762, the starting dose will remain at 80 mg once daily in combination with enzalutamide. The likelihood that GSK525762 or abiraterone will have an effect on the PK of the other is low. The AE profiles of both agents, however, contain some common toxicities. To reduce the risk of toxicity and assess the safety and tolerability of the combination, the starting dose of GSK525762 will be reduced to 60 mg once daily in combination with the approved dose of abiraterone. Lower exposures (either via lower dose or intermittent dosing) may be evaluated if the starting doses of either proves to yield unacceptable toxicity.

Summaries of findings from both clinical and non-clinical studies conducted with GSK525762 can be found in the Investigator Brochure. GSK525762 data provided in Section 4.6.3 reflects study treatment related AEs across all dose levels administered in the single-agent BET115521 solid tumor study as described in the Investigator's Brochure [GlaxoSmithKline Document Number 2011N113741_07, 2018]. The data cut-off date was 29 Jan 2018. Summaries of findings from both clinical and non-clinical studies conducted with enzalutamide/abiraterone can be found in the Food and Drug Administration (FDA) package insert. The following section outlines the risk assessment and mitigation strategy for this protocol.

4.6.3.1. Predicted Overlapping Toxicities

4.6.3.1.1. Gastrointestinal Safety Findings

Enzalutamide: As described in the enzalutamide FDA package insert (Section 6.1) [Xtandi, 2015], in two randomized clinical trials with CRPC subjects, some of the most commonly reported adverse effects per treatment arm were gastrointestinal, including constipation and diarrhea. Gastrointestinal toxicity was almost predominantly Grades 1 and 2; Grade 3 and 4 level gastrointestinal toxicity was observed in<1% subjects.

Abiraterone: As described in the abiraterone FDA package insert (Section 6.1) [Zytiga, 2015], in two randomized clinical trials with CRPC subjects, some of the most commonly reported adverse effects per treatment arm were gastrointestinal, including constipation, dyspepsia, vomiting and diarrhoea . Gastrointestinal toxicity was almost predominantly Grades 1 and 2; Grade 3 and 4 level gastrointestinal toxicity were observed in<1% subjects.

GSK525762: Gastrointestinal effects were frequently the dose-limiting toxicities in non-clinical animal studies of GSK525762. Dogs, rats and mice treated with repeated doses of GSK525762 experienced reduced body weight, ulceration/inflammation of the gastrointestinal (GI) tract, and abnormal feces. In study BET115521, drug-related GI events were reported, as well. Drug-related nausea was reported in 41%, decreased appetite was reported in 36%, diarrhea was reported in 32%, dysgeusia was reported in 30%, and vomiting was reported in 27% of subjects. Gastrointestinal toxicity was predominantly Grades 1 and 2; 5% of subjects reported Grade 3 nausea, 4% reported Grade 3 decreased appetite, 3% reported Grade 3 vomiting, and 2% of subjects reported Grade 3 diarrhea. No Grade 4 GI effects were observed.

Monitoring and Management: During clinical studies, medical history, physical examination (including weight) and clinical laboratory assessments will be used to identify and assess toxicity in the GI tract. Management guidelines are included in the protocol for gastrointestinal toxicity. In the event of clinically significant toxicity, treatment will be withheld, and supportive therapy provided according to standard medical practice.

4.6.3.1.2. Hepatic Safety Findings

Abiraterone: As described in the FDA package insert (Section 6.1), in the two randomized clinical trials, Grade 3 or 4 ALT/AST increases were observed in 4% of subjects that received abiraterone. In 1% of subjects, treatment was discontinued due to increase in liver enzymes. Subjects with elevated baseline ALT/AST experienced liver test elevation than those subjects with normal values.

GSK525762: In non-clinical animal studies, non-adverse liver changes were observed in rats, mice and dogs including increases in bilirubin levels in rats, increased bile acids in rats and mice and transient, reversible increased in AST and/or ALT in rats and dogs. Hepatocellular necrosis was observed in a single rat at a non-tolerated dose. In the BET115521 clinical trial, liver effects have been noted. Cases of liver events meeting the definition of severe liver injury based on liver chemistries (ALT ≥3X ULN and Bilirubin

≥2X ULN) have been reported in study BET115521. Additional complicating factors were reported for these cases (e.g. liver metastasis and sepsis) with liver enzymes trending towards normal levels upon stopping GSK525762. Drug related elevated blood bilirubin was reported in 24%, aspartate aminotransferase (AST) elevation was reported in 11%, and alanine aminotransferase (ALT) elevation was reported in 8% of subjects. These drug related hepatic toxicities were predominantly Grades 1 and 2; 7% reported Grade 3 and <1% reported Grade 4 blood bilirubin increased and 2% of subjects reported Grade 3 AST increase. There were no Grade 4 ALT increases noted.

Monitoring and Management: Inclusion/exclusion criteria will include hepatic eligibility criteria. All subjects will be monitored for hepatic dysfunction. Management and stopping criteria are included in the protocol as described in Appendix 2 and Section 5.4.1.

4.6.3.1.3. Hematopoietic Safety Findings

Abiraterone: As described in the FDA package insert (Section 6.1), abiraterone was associated with anemia in >2% of subjects.

GSK525762: In non-clinical studies of GSK525762, lymphoid / hematologic toxicity was observed in rats, mice and dogs and the effects contributed to the definition of severely toxic repeat dose in rats (30 mg/kg). The effects manifested as hypocellularity in bone marrow, thymus, spleen and lymph nodes; decreased spleen and thymic weight; mild hemolysis (rat); decreased white cell /lymphocyte/platelet count and variable and inconsistent changes in multiple red blood cells parameters and reticulocyte counts. Effects were generally reversible but minimal bone marrow cellularity was still evident in rats following an off-dose period.

In the BET115521 clinical trial, thrombocytopenia has been observed in subjects with solid tumors mainly at doses of 60 mg and above. Thrombocytopenia was only noted after more than a week of continuous dosing, and platelet counts recovered after cessation of the drug. Drug related thrombocytopenia was reported in 59%, anemia was reported in 29%, international normalized ratio increased was reported in 14%, prothrombin time prolonged in 12% and coagulation factor VII level decreased in 10% of subjects. These AEs were mainly Grade 1 or 2; with Grade 3 thrombocytopenia reported in 22%, Grade 3 anemia reported in 12% and Grade 3 factor VII decrease in 4% of subjects. Grade 4 thromobocytopenia was reported in 16%, anaemia in 1% and factor VII decrease in 4% of subjects.

Mild to severe hemorrhagic events have been observed during the use of GSK525762, primarily during occurrences of moderate to severe thrombocytopenia. Most events have been associated with confounding factors beyond thrombocytopenia such as disease under study, and/or with metastases to affected areas, low molecular weight heparin use and previous radiation. There have been SAEs noted of decrease in Coagulation Factor VII. Refer to IB for additional details [GlaxoSmithKline Document Number 2011N113741_07, 2018].

Monitoring and Management: Inclusion/exclusion criteria will require appropriate baseline hematologic and coagulation values prior to enrolment. Subjects will undergo

frequent complete blood count (CBC) measurements, and management guidelines (Appendix 2) are included in the protocol to guide dose interruption/reduction decisions.

4.6.3.1.4. General Toxicity Findings

Enzalutamide: As described in the enzalutamide FDA package insert (Section 6.1), in two randomized clinical trials with CRPC subjects, asthenia/fatigue were reported as a more common adverse reaction in both studies. In study 1, subjects with mCRPC following chemotherapy, all grades of asthenia/fatigue occurred more commonly (≥2% over placebo; 50.6% vs. 44.4%). In this study, the occurrence of Grade 3-4 AEs was similar in both the enzalutamide and placebo arms. In study 2, subjects with chemotherapy-naive mCRPC, all grades of asthenia/fatigue occurred more commonly (≥2% over placebo; 46.9% vs. 33.0%). In this study, the occurrence of Grade 3-4 was similar in both the enzalutamide and placebo arms. It was noted that this was the most common AE leading to treatment discontinuation which occurred in 1% of subjects in both arms.

Abiraterone: As described in the FDA package insert (Section 6.1), abiraterone was associated with fatigue in >2% of subjects.

GSK525762: In the BET115521 study, 25% of subjects reported fatigue and 24% reported asthenia. Most of these AEs were Grade 1 or 2; with Grade 3 asthenia reported in 9% and Grade 3 fatigue in 3% of subjects. No Grade 4 asthenia/fatigue AEs were reported.

Monitoring and Management: Medical and previous therapy history will be used to identify and assess whether these effects have been previously experienced by subjects, the severity and if withholding ADT was required. These affects are generally managed by rest and withholding treatment if fatigue is intolerable.

4.6.4. Predicted Single-Agent Toxicities

4.6.4.1. Cardiovascular Safety Findings

GSK525762: Reversible changes in the corrected QT (QTc) interval were noted in dogs in single- and repeated-dose studies. In addition, reversible increases in biomarkers of cardiac damage (cardiac troponin T, myosin light chain and/or cardiac troponin I) were also seen in the rat and dog. Despite these QTc and cardiac biomarker changes, there was no evidence of compound-related myocardial necrosis or other histopathological changes in cardiac tissue of either species.

An internal safety review of categorical analysis of QTc increase (and decrease) from baseline of 271 subjects dosed up to 100 mg in the BET115521 and up to 120 mg in the BET116183 clinical trials demonstrated a clinically negligible effect on QTc. Based on this analysis, the entry and stopping criteria have been modified.

Monitoring and Management: Subjects will be monitored closely for changes in QTc with 12-lead ECG and for elevations in plasma troponin. Safety ECGs will be performed at the time points specified in Time and Events tables (Section 7.1) using a standard 12-lead ECG machine that automatically calculates the heart rate (HR) and measures PR, QRS, QT and QTcF intervals. As clinically indicated, the mean from triplicate ECGs will

be evaluated. Safety ECGs will be reviewed by the investigator on an ongoing basis for safety purposes. Dosing should not begin until the safety ECG has been reviewed and no significant abnormalities have been detected.

To monitor for cardiomyopathy, echocardiograms will be performed at the time points specified in the Time and Events tables (Section 7.1). Management guidelines (Appendix 2) and stopping criteria (Section 5.4.2 and Section 5.4.3) are incorporated in the protocol.

Laboratory evaluations for cardiac troponins and electrolytes (including potassium and magnesium) will be performed at baseline and at regular intervals (as specified in the Time and Events tables), and when clinically warranted during the study treatment. Troponin I or T (based on availability) levels will be tested by a local laboratory. Appropriate medical therapy will be provided by the investigator for any clinically significant increase in troponins including withholding or discontinuing the study medication. Appropriate medical management will be instituted to assure that electrolytes are kept within the normal range.

4.6.4.2. General toxicities

Enzalutamide: As described in the enzalutamide FDA package insert, any enzalutamide related toxicities, as determined by the Investigator, will require at least a one week hold of enzalutamide until a return to ≤Grade 2 toxicity.

Monitoring and Management: Subjects will be monitored according to the management guidelines (Appendix 2).

4.6.4.3. Seizure

Enzalutamide: As described in the enzalutamide FDA package insert (Section 6.1), in two randomized clinical trials with CRPC subjects, 7 of 800 (0.9%; study 1) and 1 of 871 (0.1%; study 2) subjects experienced seizure.

Monitoring and Management: Exclusion criteria include history of seizure or any condition that may predispose subject to seizure (e.g., prior cortical stroke or significant brain trauma), and subjects will be monitored. Enzalutamide should be permanently discontinued in subjects who develop a seizure during treatment.

4.6.4.4. Posterior Reversible Encephalopathy Syndrome (PRES)

Enzalutamide: As described in the enzalutamide FDA package insert (Section 6.1), there have been reports of PRES in subjects receiving enzalutamide.

Monitoring and Management: Subjects will be monitored according to the management guidelines and brain magnetic resonance imaging (MRI) is mandated if clinically required. Enzalutamide should be permanently discontinued in subjects who develop a seizure during treatment.

4.6.5. Risk Assessment

The toxicities listed below are a summary of those most likely to be observed in clinical practice, or are of special interest. For a full list of predicted and observed toxicities, refer to the GSK525762 IB and the FDA package insert for enzalutamide/abiraterone.

4.6.6. Benefit Assessment

Study 204697 is a Phase I dose-escalation and expansion study, and the first comparative study of a BET inhibitor in combination with the next generation AR-targeting agents abiraterone or enzalutamide in men with metastatic or advanced CRPC who have progressed on abiraterone or enzalutamide.

Both GSK525762 and abiraterone/enzalutamide have been administered as single agents to men with mCRPC. Abiraterone and enzalutamide are currently approved as single agent to treat mCRPC. Data from the first in human study with GSK525762 used as a single agent to treat late stage mCRPC subjects is preliminary, but indicates at least minimal activity as evidenced by fluorodeoxyglucose (FDG)-positron emission tomography (PET) response and decrease in bone pain. Additional data is being collected at the single agent RP2D.

Study 204697 is based on the hypothesis that adding the BET inhibitor GSK525762 to androgen deprivation therapy (ADT) will overcome resistance to ADT. If successful, the main benefits are two-fold – i) provides a new treatment regimen for mCRPC that will be an added option for treatment of subjects who fail single agent ADT and may prolong survival; ii) for mCRPC patient who fail first line ADT, the scope to delay chemotherapy.

4.6.7. Overall Benefit: Risk Conclusion

The adverse event profile for abiraterone and enzalutamide are well known and guidance is available on the label for dose modification in the event of defined AEs. The adverse event profile of GSK525762 is evolving, but data is available from more than 150 subjects treated and management algorithms are available for the most common as well as serious AEs. Totality of the data indicates that overlapping toxicity in combination will most likely be hepatotoxicity, for which monitoring and stopping rules are built into the study. Extensive PK sampling and adverse event profile will be used to determine dosing levels and RP2D. If any one of the combinations is found to be tolerable and meeting efficacy targets set out in the study, then a randomized controlled Phase 2 study will be designed to establish the benefits outlined the Section above. This may provide additional lines of treatment for subjects with mCRPC who progress on current regimens based on ADT.

Taking into account the measures taken to minimise the risk to subjects participating in Phase I clinical trials, and potentially enriching for CRPC subjects who may respond to the combination of a BET inhibitor and an AR antagonist, the potential risks identified in association with GSK525762 and abiraterone/enzalutamide are justified by the anticipated benefits that may be afforded to subjects with advanced or metastatic CRPC, who have failed prior therapies.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB/IB supplement(s) for GSK525762 and the enzalutamide/abiraterone product label.

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

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Written informed consent provided
2. Males ≥18 years of age (at the time written consent is obtained for screening)
3. Histologically confirmed adenocarcinoma of the prostate:
    a. Screening and on-treatment biopsy is mandatory. If adequate number of paired biopsy samples are collected (≥ 20 paired samples for each dose level in each Arm, unless an Arm is closed early), then further biopsy sampling will be considered based on available data.
    b. Screening biopsy can be waived if patient had a recent biopsy after failure of the most recent therapy (within 30 days) and the biopsy sample is secured to be sent as screening biopsy for this study.
4. Surgically or medically castrated, with testosterone levels of ≤ 50 ng/dL (<2.0 nM). If the patient is being treated with LHRH agonists/antagonists (patient who have not undergone orchiectomy) this therapy must have been initiated at least 4 weeks prior to Week 1 Day 1 and must be continued throughout the study.
5. Subjects must have failed prior therapy with abiraterone, enzalutamide, or both
    a. Has completed at least 12 weeks of prior continuous therapy with abiraterone or enzalutamide in any prior line
    b. Lead-in dosing period for enzalutamide only will be required under the following circumstance:
        i. If the subject has enzalutamide discontinuation for >7 days prior to dosing start with GSK525762 plus enzalutamide on trial, then an enzalutamide only lead-in dosing of 28 days is required
        ii. If the subject has enzalutamide discontinuation for ≤7 days prior to dosing start with GSK525762 plus enzalutamide on trial, then an enzalutamide only lead-in dosing of 14 days is required

iii. If the subject is on continuous dosing with enzalutamide prior to dosing start with GSK525762 plus enzalutamide on trial, then subject can start on combined dosing at end of screening period.

c. Lead-in dosing period for abiraterone only will be required under the following circumstance:

i. If the subject has abiraterone discontinuation for more than 3 days prior to dosing start with GSK525762 plus abiraterone on trial, then an abiraterone only lead-in dosing of 7 days is required

6. One to two line(s) of prior taxane-based chemotherapy allowed. If docetaxel chemotherapy is used more than once, this will be considered as one regimen. Subjects who have not received prior chemotherapy in any setting will qualify for study if they are ineligible for or refuse chemotherapy.
7. Documented prostate cancer progression as assessed by the investigator with one of the following:

a. PSA progression defined by a minimum of 3 rising PSA levels with an interval of ≥1 week between each determination. The PSA value at screening must be ≥5 ug/L (5 ng/mL) if PSA is the only indication of progression; subjects on systemic glucocorticoids for control of symptoms must have documented PSA progression by PCWG3 while on systemic glucocorticoids prior to commencing Week 1 Day 1 treatment.

b. Radiographic progression of soft tissue disease by PCWG3-modified RECIST 1.1 (Appendix 5) criteria or bone metastasis with 2 or more documented new bone lesions on a bone scan/ CT scan with or without PSA progression

8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
9. Life expectancy > 12 weeks
10. Able to swallow and retain orally administered medication
11. Adequate organ function as defined in Table 5.

Table 5 Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
White blood cells	>3 X 10^9/L
Absolute neutrophil count (ANC)	≥ 1.5 X 10^9/L
Hemoglobin	≥ 9 g/dL (subjects that required transfusion or growth factor need to demonstrate stable hemoglobin for 7 days of 9 g/dL)
Platelets	≥ 100 X 10^9/L
Prothrombin time (PT)/International normalized ration (INR) and Partial thromboplastin time (PTT)	≤ 1.5 X upper limit of normal (ULN)
Hepatic	
Albumin	≥2.5 g/dL
Total bilirubin	≤ 1.5 x ULN[a]
Aspartate transaminase (AST)	≤2.5 × ULN
Alanine transaminase (ALT)	≤2.5 × ULN OR <5x ULN is acceptable for subjects with documented liver metastases/tumor infiltration
Renal	
Creatinine OR Creatinine clearance [either directly measured or calculated by Cockcroft-Gault formula[b]]	≤1.5 X ULN the institutional upper limit of normal ≥ 50 mL/min
Cardiac	
Ejection fraction Troponin (I or T)	≥ LLN by echocardiogram or MUGA and minimum of 50% LVEF ≤ ULN
Other	
Testosterone	≤50 ng/dL

a. Isolated bilirubin >1.5 X ULN is acceptable if bilirubin is fractionated and direct bilirubin <35% or subject has a diagnosis of Gilbert's syndrome

b. Refer to Appendix 4 for Cockcroft-Gault formula

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

12. Male Participants: Contraceptive use by men or female partner should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

    Male participants are eligible to participate if they agree to the following during the intervention period and for at least 16 weeks after the last dose of study treatment:

    - Refrain from donating sperm

    PLUS either:

- 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.

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.

12. History of seizure within 6 months of study treatment initiation or any condition that may predispose subject to seizure (e.g., prior cortical stroke or significant brain trauma) or who are currently being treated with cytochrome P450 enzyme inducing anti-epileptic drugs for seizures (use of anti-epileptic drugs to control pain is allowed in subjects not suffering from seizures unless drug is excluded due to CYP3A4 induction - phenytoin, carbamazepine, phenobarbital (see Section 6.11.1).
13. History of loss of consciousness or transient ischemic attack within 12 months prior to enrollment
14. Subjects with symptomatic or impending cord compression unless appropriately treated beforehand and clinically stable and asymptomatic.
15. Current use of a prohibited medication or planned use of any forbidden medications during treatment with GSK525762 and abiraterone/enzalutamide. This includes medications that are potent inducers or inhibitors of CYP3A4 enzymes or strong inhibitors of CYP2C8 (see Section 6.11.2 for the list of prohibited medications).
16. Subjects with gastrointestinal disorders likely to interfere with absorption of the study medication
17. Subjects with known bleeding diathesis will be excluded from the study.
18. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases or otherwise stable chronic liver disease per investigator assessment).
19. Initiating bisphosphonate or denosumab therapy or adjusting dose/regimen within 3 months prior to Week 1 Day 1. Subjects on a stable bisphosphonate or denosumab therapy are eligible and may continue.
20. Any serious known immediate or delayed hypersensitivity reaction to GSK525762 or idiosyncrasy to drugs chemically related to the investigational drugs. Additionally, any known hypersensitivity to either enzalutamide, abiraterone or any excipients would be excluded.
21. Known history of human immunodeficiency virus (HIV)
22. Presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening.

    NOTE: Subjects with positive hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative hepatitis C RNA PCR is obtained.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (Appendix 8). Run-in failures are defined as subjects who start the run-in of either abiraterone or enzalutamide and withdraw from this run-in and do not proceed to dose with GSK525762.

5.4. Withdrawal/Stopping Criteria

Subjects will receive study treatment until disease progression, death or unacceptable adverse event, including meeting stopping criteria for liver chemistry, hematologic/non-hematologic toxicity, QTc prolongation, or left ventricular ejection fraction (LVEF)/valvular dysfunction as defined in Section 5.4.1 through Section 5.4.3. Subjects may be permitted to continue on therapy in the setting of equivocal progression (e.g., rising tumor markers early in therapy in the absence of confirmed radiographic progression, or equivocal radiographic imaging as described in Appendix 5) provided that the subject is not experiencing significant toxicity, the investigator believes (and the medical monitor concurs) that the subject may continue to receive benefit, and the subject has no other reasonable option for therapy that will provide long-term control of disease.

In addition, study treatment may be permanently discontinued for any of the following reasons:

- deviation(s) from the protocol
- request of the subject or proxy (withdrawal of consent by subject or proxy)
- investigator's discretion
- subject is lost to follow-up
- study is closed or terminated
- a dose delay of >14 days unless the investigator and Medical Monitor agree that further treatment may benefit the subject
- A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. All subjects who discontinue from study treatment will have safety assessments at the time of discontinuation and during post-study treatment follow-up as specified in Time and Events Table (Section 7.1).
- If a subject withdraws consent from the study, no further assessments will be completed, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

The primary reason study treatment was permanently discontinued must be documented in the subject's medical records and electronic case report form (eCRF).

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

Once a subject has permanently discontinued from study treatment, the subject will not be allowed to be retreated.

During dose escalation, specific dosing regimen(s) may be terminated if they are unable to be tolerated in an acceptable proportion of subjects. These regimen(s) will not be carried forward into expansion phase. Any subject receiving a terminated regimen may continue to receive that regimen, so long as that subject does not experience unacceptable toxicity, or else be switched to a previously cleared dose at the discretion of the investigator after discussion with the medical monitor.

During dose expansion, unless a dose level is closed early, survival follow-up will continue in each cohort until approximately 70% of the total number of subjects have progressed or died. At such time, all cohorts will be closed and any further follow-up on subjects enrolled in each cohort will cease.

Subjects who require permanent discontinuation of either abiraterone or enzalutamide the given combination may continue GSK525762 as a single agent if there is evidence of continuing benefit on treatment until disease progression, withdrawal of consent, unacceptable toxicity, or closure of the study.

At the time of study completion, subjects with radiologically confirmed lack of disease progression (dose escalation and expansion phase) who are still receiving GSK525762 and/or abiraterone/enzalutamide may continue treatment through a separate mechanism (e.g., roll-over protocol) to be determined at that time.

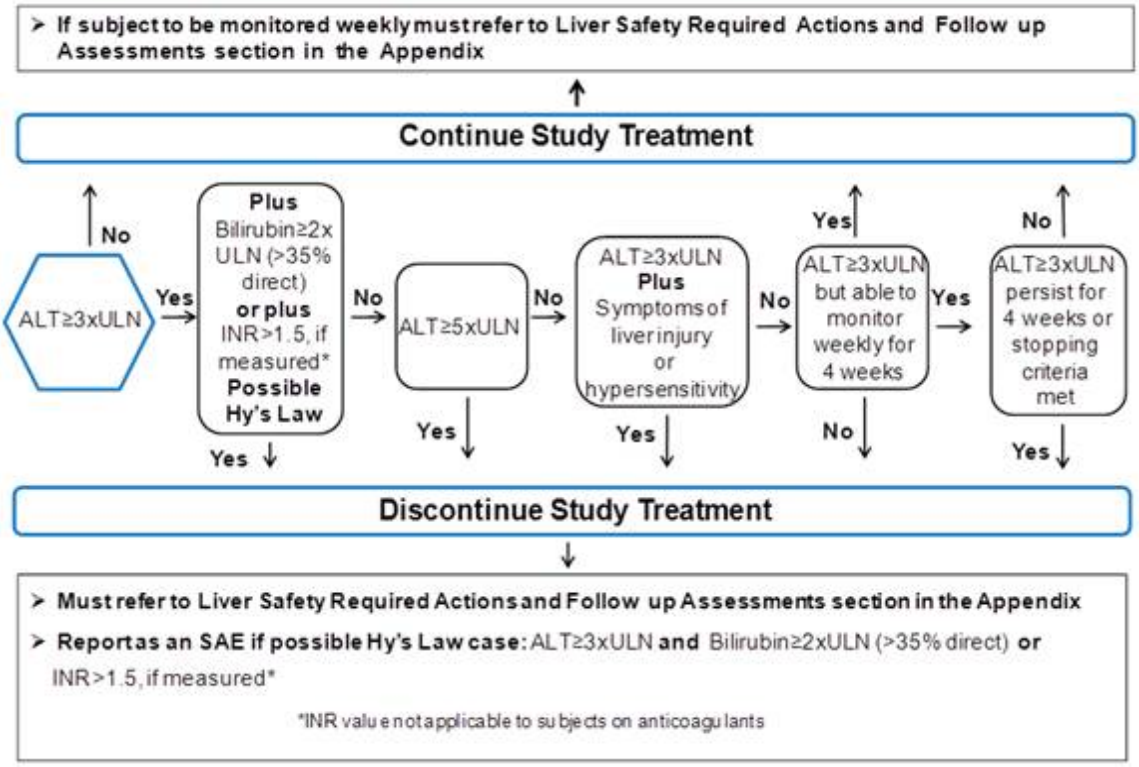
5.4.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

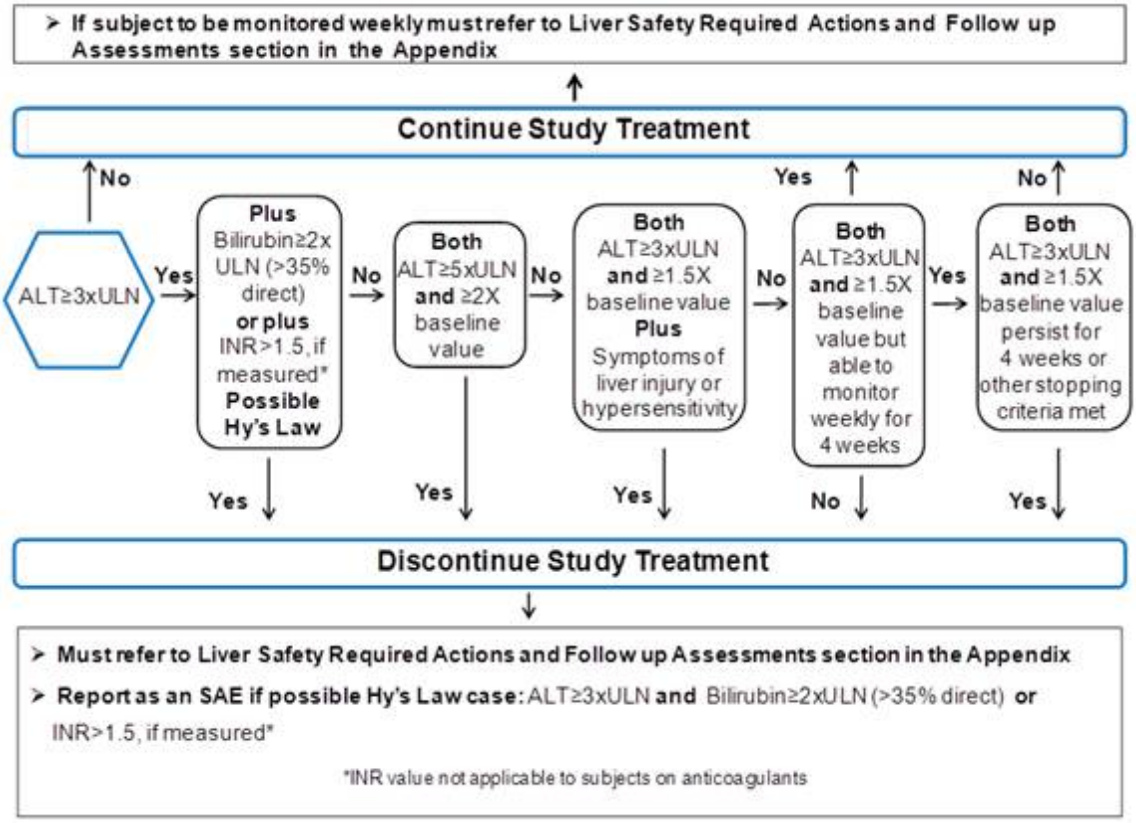
See Figure 6 and Figure 7 for liver stopping criteria for subjects without and with liver metastases, respectively. The algorithms are best read from left to right.

Figure 6 Phase I/II Liver Chemistry Stopping and Increased Monitoring Algorithm for Subjects WITH entry criteria ALT ≤2.5xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6

Figure 7 Phase I/II Liver Chemistry Stopping and Increased Monitoring Algorithm including Subjects WITH documented liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5xULN but ≤5xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

5.4.1.1. Study Treatment Restart or Rechallenge

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

- GSK Medical Governance approval **is granted**
- Ethics and/or Institutional Review Board (IRB) approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

Refer to Appendix 7 for full guidance.

In France, if stopping criteria is met, subjects will not be allowed to restart or be rechallenged.

5.4.2. QTc Stopping Criteria

For the purposes of this study, the corrected QT (QTc) is the QT interval corrected for heart rate according to Fridericia's formula (QTcF; defined as [QT/($RR^{1/3}$)]). QTcF will be used for all subjects for purposes of eligibility, data analysis, and withdrawal. The QTcF should be based on averaged QTcF values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

Study treatments will be withheld if either of the following occurs:

- QTcF interval ≥500 msec AND ≥60 msec change from baseline
- QTcF interval ≥530 msec AND <60 msec change from baseline

In either case, both GSK525762 and abiraterone/enzalutamide will be discontinued unless the benefits of therapy outweigh the risk of rechallenge in the opinion of the investigator, the Medical Monitor, as well as GSK medical governance. In this situation, rechallenge may be permitted (see Appendix 2 for rechallenge guidelines).

In France, if stopping criteria is met, subjects will not be allowed to restart or be rechallenged.

5.4.3. Left Ventricular Ejection Fraction (LVEF) Stopping Criteria

Echocardiography (ECHO) or MUGA scan must be performed at Screening and periodically throughout the study as outlined in the Time and Events Table (Section 7.1). Please refer to the LVEF management guidelines in Appendix 2 of the protocol for further detail.

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

5.4.4. Other Stopping Criteria

To monitor for hematologic toxicity, CBCs will be drawn twice during the first week (includes screening), weekly for the next four weeks of study, and then every four weeks, as described in the Time and Events table. Subjects who develop Grade 3 or greater anemia or thrombocytopenia may be monitored more frequently, as clinically indicated. Please see Appendix 2 for suggested management of hematologic toxicity.

Safety will be reviewed on an ongoing basis by the Safety Review Team (SRT) which will be compromised of, at a minimum, a medical monitor, GSK Global Safety representative, and clinical study representative (including a representative from Biostatistics). All events of potential causality, including deaths, SAEs, and Grade 3/4 adverse events, will be carefully evaluated.

If clinically significant adverse events or toxicities are observed in more than one third of the subjects, and/or if deaths related to study drug are observed, enrollment may be terminated and/or a lower-dose cohort may be opened or expanded.

5.5. Subject and Study Completion

A subject will be considered to have completed the study if they are followed until death.

Subjects who have not died, and are no longer being followed for survival are considered to have discontinued the study. The End of Study eCRF should only be completed when a subject is no longer being followed. The study will be considered completed for purposes of a final analysis when 70% of evaluable subjects enrolled have progressed or died. If available, subjects continuing on GSK525762 at the time of final analysis may be offered the option to continue it through another mechanism (eg, in a rollover trial).

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.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

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

Investigational Product						
Product name:	GSK525762 Besylate Tablets			Abiraterone acetate		Enzalutamide
Unit dose strength(s)/Dosage level(s):	5 mg[a]	25 mg[a]	20 mg[a]	250 mg	500 mg[b]	40 mg
Dosage form	Tablet	Tablet	Tablet	Tablet	Tablet	Tablet
Manufacturer	GSK	GSK	GSK	Janssen	Janssen	Astellas
Physical description:	White to slightly colored, round, biconvex tablets with no markings, film-coated tablet		Yellowish-pink, round, biconvex tablets with no markings, film-coated	White to off-white, oval tablets debossed with AA250 on one side	Film-coated, purple oval tablets debossed with AA on one side and 500 on the other side	White to off-white oblong soft gelatin capsules imprinted in black ink with ENZ
Route/ Administration/ Duration:	**Oral;** see Time and Event Tables for schedule and administration timings			**Oral;** see Time and Event Tables for schedule and administration timings		**Oral;** see Time and Event Tables for schedule and administration timings
Dosing instructions:	Dose with 240 mL water and should be taken around the same time every day without regards to timing of meal (If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.)			Dose with 240 mL water and should be taken on an empty stomach, and no food should be consumed from 2hrs before the dose until 1hr after the dose. Dose 5 mg prednisone orally twice daily as per prescribing information.		Dose with 240 mL water and should be taken around the same time every day without regards to timing of meal (If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.)

NOTE: These formulation details are current at the time of protocol finalization and may be updated in other documents (e.g., SRM and/or informed consent form) without requiring protocol amendment

a. The 20 mg tablet formulation is in development and will be utilized during the planned duration of the study. The 5 mg and 25 mg tablet formulation may be discontinued when the 20 mg tablet formulation is available. The use of 20 mg tablets will require regulatory authority approvals.
b. The 500 mg tablet may be supplied dependent on the availability by Janssen. The use of 250 mg tablet formulation may be discontinued when 500 mg tablet is available

6.2. Treatment Assignment

Subjects will be assigned to receive GSK525762 and abiraterone/enzalutamide in an open-label fashion. Subjects will be identified by a unique subject number that will remain consistent for the duration of the study.

For Arm A, during the initial evaluation of DL60, approximately 3 to 10 subjects will be enrolled until it is determined that DL60 does not exceed the MTD. 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 schedule, 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 intermittent dosing at 60 mg dose

level (DL60 ALT) and/or a lower daily dose level (DL-1, 40 mg) may be evaluated). If DL60 has been cleared in dose escalation, approximately 6 to 10 subjects will be enrolled in the DL80 cohort for evaluation of dose escalation. 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. Subjects enrolled during dose escalation will continue treatment and will not roll into dose expansion.

To further explore and identify the MTDs (and RP2Ds), the two most tolerable dose levels may be randomized into 2 expansion cohorts and will be based on prior lines of therapy (L2 or Lx). A maximum of up to 30 subjects each (in addition to those enrolled in dose escalation) will be enrolled into each dose level cohort.

If either dose level cohort is filled or terminated, then all subjects will be enrolled in the remaining prior treatment-specific cohort until it is filled or terminated.

For Arm B, as enzalutamide is a known CYP3A4 inhibitor, and DDI could potentially lower the exposure of GSK525762 levels, the planned dose levels are expected to provide equivalent doses similar to those being examined in Arm A.

During the initial evaluation of DL80, approximately 3 to 10 subjects will be enrolled until it is determined that DL80 does not exceed the MTD. 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 schedule, either at a dose level where daily treatment may be intolerable or at a lower dose. For example, if DL80 exceeds the maximum permitted toxicity rate, then intermittent dosing at 80 mg dose level (DL80 ALT) and/or a lower daily dose level (DL-1, 60 mg) may be evaluated. If DL80 has been cleared in dose escalation, approximately 3 to 10 subjects will be enrolled in the DL100 cohort until it is determined that DL100 does not exceed the MTD. 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.

An additional dose level, DL120, may be initiated after careful review of the PK and safety data from the DL80 and DL100 dose levels. If the DL120 cohort is opened, it will enrol approximately 3 to 10 subjects until it is determined whether DL120 does not exceed the MTD. Subjects enrolled during dose escalation will continue treatment and will not roll into dose expansion.

To further explore and identify the MTDs (and RP2Ds), the two most tolerable dose levels may be initiated and eligible subjects may be randomized by prior lines of therapy (L2 or Lx). A maximum up to 30 subjects each (in addition to those enrolled in dose escalation) will be enrolled into each dose level cohort. If only one dose level is tolerable for dose expansion, subjects will be enrolled and not randomized.

6.3. Planned Dose Adjustments

There are no pre-planned dose adjustments per protocol. Dose reductions for individual subjects may be required, based on toxicity observed during the study (please refer to Appendix 2), and the frequency and duration of dose reductions will be reported. Table 6 clarifies the dose reductions for GSK525762 at any planned study dose.

Table 6 GSK525762 Dose Reductions

Current GSK525762 Dose:	If subject requires dose level reduction:
40 mg	No further dose reduction allowed
60 mg	40 mg
80 mg	60 mg
100 mg	80 mg
120 mg	100 mg

If enzalutamide is discontinued for more than or equal to 7 days, then the dose of GSK525762 should be reduced one dose level and the maximum dose of GSK525762 should be the single agent RP2D of 80 mg. If enzalutamide is re-started, GSK525762 should remain at the reduced dose level or the maximum single agent RP2D of 80 mg until after at least 14 days until the dose is escalated, if applicable. Subjects who require permanent discontinuation of either abiraterone or enzalutamide in the combination may continue GSK525762 as a single agent if there is evidence of continuing benefit on treatment. If GSK525762 is continued as a single agent, the maximum dose would be 80 mg. Intra-subject dose escalations from the planned starting dose during dose escalation will not be permitted. Intra-subject dose escalation may be permitted during dose expansion for the lower dose level only if that dose is determined to be futile.

Based on dose table (Table 6) and effect of enzalutamide on GSK525762, no dose level/schedule of less than 40 mg QD will be allowed for Arm B. If a subject is on an alternate dosing schedule and requires a de-escalation to 40 mg, then the subject must move to 40 mg QD.

During any dose interruption of GSK525762, abiraterone or enzalutamide may be continued at the protocol dose unless dose interruption of these combination products is also required. If GSK525762 is permanently discontinued, subject must be discontinued from the abiraterone or enzalutamide treatment and withdrawn from the study.

6.4. Blinding

This is an open-label study which does not require blinding.

6.5. Packaging and Labeling

GSK525762 and abiraterone/enzalutamide will be provided to the sites by GSK. Prednisone will not be supplied by GSK. The contents of the labels will be in accordance with all applicable regulatory requirements.

6.6. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.

Limited exposure and precautionary action (e.g., wearing gloves, washing hands post exposure, etc.) should be taken by site staff dispensing GSK525762. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.7. Compliance with Study Treatment Administration

At each visit, an evaluation of subject compliance with taken medication will be performed. The investigator will make every effort to bring non-compliant subjects into compliance.

When subjects are dosed with GSK525762 or abiraterone/enzalutamide at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

Compliance of study treatment administration will be assessed through querying the subject during the site visits, review of subject dosing diaries and documented in the source documents and eCRF.

A record of the number of GSK525762 and abiraterone/enzalutamide tablets dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the eCRF.

6.8. Treatment of Study Treatment Overdose

For this study, any dose of GSK525762 or abiraterone/enzalutamide greater than the protocol-specified dose within a 24 hour time period (± 4 hours) will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose the investigator (or treating physician) should:

- Contact the Medical Monitor immediately
- Closely monitor the subject for AEs/SAEs and laboratory abnormalities until GSK525762 and/or abiraterone/enzalutamide can no longer be detected systemically (at least 28 days)
- Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis)
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.9. Treatment after the End of the Study

Post study treatment will not be provided as part of the protocol. Upon discontinuation from assigned study treatment, subjects may receive additional (non protocol) therapy at the discretion of the treating physician. New anti-cancer therapy should be documented on the eCRF. Every effort should be made to complete the required withdrawal and follow up evaluations prior to initiating further therapy or dosing of an investigational agent (see Section 7.1 for follow-up assessments and procedures).

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

6.10. Lifestyle and/or Dietary Restrictions

6.10.1. Dietary Restrictions

Abiraterone will be administered with no food for 2 h before and 1 h after each dose, whereas Enzalutamide can be taken under fasting or fed conditions. GSK525762 can be taken under fasting or fed conditions, except on serial PK sampling days (Week [W] 1 Day [D] 1 and W3D1) for at least 12 subjects at each dose level, as described below.

Subjects should abstain from consumption of Seville oranges, grapefruit, grapefruit hybrids or grapefruit juice and/or pomelos, exotic citrus fruits, from one day prior to the first dose of study treatment until the last dose of study drug.

If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.

On serial PK sampling days (W1D1 and W3D1 for at least 12 subjects at each dose level), subjects should fast overnight (i.e., at least 8 hours) and should continue fasting until at least 2 hours after administration of GSK525762. Fasting will consist of avoiding the oral ingestion of calorie-containing products; however, ingestion of water is permitted.

6.11. Concomitant Medications and Non-Drug Therapies

Subjects will be instructed to inform the investigator prior to starting any new medications from the time of first dose of study treatment until the end of the study (Final Study Visit). Any concomitant medication(s), including non-prescription medication(s) and herbal product(s), taken during the study will be recorded in the eCRF. The minimum requirement is that drug name, dose and the dates of administration are to be recorded. Additionally, a complete list of all prior anti-cancer therapies will be recorded in the eCRF.

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

If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by GSK and stored in the study file. Any such changes will be communicated to the investigative sites in the form of a letter.

6.11.1. Permitted Medications and Non-Drug Therapies

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate. The only caveat is that subjects should not receive those medications listed as prohibited in Section 6.11.2.1.

Bisphosphonates and denosumab will be allowed if subjects have been on a stable dose for at least three months prior to receiving the first doses of GSK525762 and abiraterone/enzalutamide.

6.11.2. Prohibited Medications and Non-Drug Therapies

6.11.2.1. Prohibited Medications

Subjects should not receive other anti-cancer therapy [including chemotherapy, immunotherapy, biologic therapy, investigational therapy, or hormonal therapy (other than leuprolide or other luteinizing hormone-releasing hormone (LHRH) agonists/antagonists)] while on treatment in this study. Requirement for additional systemic anti-cancer therapy will necessitate permanent discontinuation of study drugs.

Subjects may continue to use Aspirin, but doses are not allowed to be greater than 81 mg per day (or 100 mg, as per country standards). The use of non-steroidal anti-inflammatory drugs (NSAIDs) will be excluded, except for when NSAIDs will provide benefit over other analgesics and then to be used with caution including concomitant use of proton pump inhibitors.

Subjects taking enzyme-inducing antiepileptic agents or other potent inhibitors or inducers of CYP3A4 enzymes should be transitioned to another agent at least 14 days (or 5 half-lives, whichever is longer) prior to the first dose of study agents.

Anticoagulants at therapeutic doses (e.g., warfarin, direct thrombin inhibitors, etc.) are PROHIBITED from seven days prior to the first dose of study drug through completion of the End of Treatment visit. Low dose (prophylactic) anticoagulants are permitted provided that the subject's PT/PTT values meet entry criteria.

As described in Section 4.6, enzalutamide is an inducer of CYP3A, CYP2C9 and CYP2C19 at therapeutic concentrations. Medications that have a narrow therapeutic index and that are substrates of CYP3A or CYP2C9 or CYP2C19 should be avoided, as their metabolism may be affected by co-administration with enzalutamide and result in decreased exposure.

6.11.2.2. Prohibited Non-Drug Therapies

Non-drug anti-cancer therapies (e.g., radiation therapy, surgery, and/or tumor embolization) will not be permitted from the screening visit through the post-study follow-up visit.

> **NOTE**: Subjects may receive focal palliative (e.g., for management of pain or other local symptom) radiation treatment and/or surgical intervention during this study. Target lesions used for response assessment may not receive focal palliative therapy. Any proposed focal therapy must be approved by the investigator and the Medical Monitor prior to intervention.

Subjects will abstain from using herbal preparations/medications throughout the study until the final study visit. Herbal products include, but are not limited to: St. John's Wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, ginseng, and marijuana.

6.11.2.3. Cautionary Medications

Subjects should minimize the use of medications which contain acetaminophen.

If a subject requires medication for hyperemesis, due to the potential of serotonin 5-HT3 receptor antagonists to increase QTcF, palonosetron (administered per the prescribing information) and oral ondansetron (up to a maximum oral dose of 8 mg TID) are the only allowed drugs in this class (dolasetron and granisetron are not permitted). Drugs with a low risk of causing QTc prolongation (e.g., aprepitant) may be used without restriction.

Co-administration of GSK525762 and medications which may have an increased risk of Torsades de Pointes requires extreme caution beginning 14 days prior to the first dose of study drug until discontinuation from the study. Please reference current list of medications at crediblemeds.org.

After starting cautionary medications such as any listed in the referenced internet link, it is recommended that ECGs are implemented daily until the steady state of the new medication is reached. If there are ECG abnormalities, implement additional cardiotoxicity monitoring as addressed Appendix 2.

As described in Section 4.6, abiraterone is an inhibitor of CYP2C8 and CYP2D6 at therapeutic concentrations. Medications that have a narrow therapeutic index and that are

substrates of CYP2C8 or CYP2D6 should be administered with caution, as their metabolism may be affected by co-administration with abiraterone and result in increased exposure. These include thiazolidinediones (e.g., rosiglitazone, pioglitazone) and repaglinide and thioridazine.

GSK525762 is a moderate CYP3A4 inducer. Medications that have a narrow therapeutic index and that are substrates of CYP3A4 should be administered with caution, as their metabolism may be affected by co-administration with GSK525762 and result in decreased exposure. These include alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, and theophylline.

GSK525762 is a substrate for breast cancer resistance protein (BCRP) and P-glycoprotein (Pgp) transporters. Therefore, potent inhibitors of these transporters, such as cyclosporine, tacrolimus, or ketoconazole, should be avoided.

GSK525762 is an inhibitor of organic anion transporter 1A1 (OAT1) and organic anion transporter 3 (OAT3) in vitro. Substrates of these transporters include agents such as methotrexate, penicillin G, and indomethacin. While co-administration of these agents with GSK525762 is not prohibited, they should be used with caution and additional monitoring for adverse effects should be utilized.

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

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1.

The following points must be noted:

- If assessments are scheduled for the same nominal time, the assessments should occur in the following order:
    1. 12-lead ECG
    2. vital signs
    3. blood draws

  Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.
- The timing and number of planned study assessments may be altered during the course of the study based on newly available data to ensure appropriate monitoring.

- 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.

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]														

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.

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.

Table 8 Dose Escalation Time and Events, Laboratory Assessments

	SCR	Week 1		Week 2		Week 3		Week 4	Week 5	Week 6	q2w	q4w	q4w	q12w	EOT
		D1	D4	D1	D4	D1	D4	D1	D1	D1	W7 and 11	W9 to W49	W49 and thereafter	W49 and thereafter	
Clinical chemistry	X	X	X	X		X		X	X	X[2]	X[2]	X	X[2]	X	X
Hematology	X	X	X	X	X	X	X	X	X	X[2]	X[2]	X	X[2]	X	X
Liver chemistry	X	X	X	X	X	X	X	X	X	X[2]	X[2]	X	X[2]	X	X
Troponin, N-terminal pro–B-Type natriuretic peptide (NT- proBNP)	X	X	X	X	X	X	X	X	X			X		X	X
Coagulation	X	X	X	X		X		X	X	X[2]	X[2]	X	X[2]	X	X
Factor VII Assay[1]	X					X			X						
HbA1c	X								X			X		X	X
Fasting lipids	X								X			X		X	X
Thyroid stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4))[3]	X								X			X		X	X
Pancreatic Markers	X	X		X		X		X	X			X		X	X
Urinalysis	X	X		X		X		X	X			X		X	X
HIV, Hepatitis B surface antigen (HBsAg), Hepatitis C Virus (HCV) Antibody	X														
PSA[2]	X														
Testosterone	X														X

1. In addition to scheduled timepoints, perform if PT or INR or aPTT are ≥1.5XULN, or in case of a bleeding event.
2. **With the implementation of amendment 04, samples for PSA will no longer be collected. Disease assessment should be managed according to local standard of care.**
3. TSH testing is mandatory. T4 testing is only required if TSH is abnormal. T3 testing is required when clinically applicable (if both TSH and T4 are abnormal).

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

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.

Table 10 Dose Expansion Time and Events, Laboratory Assessments

	SCR	Week 1 D1	Week 2 D1	Week 3 D1	Week 4 D1	Week 5 D1	Week 6 D1	q2w W7 and 11	q4w W9 to W49	q4w W49 and thereafter	q12w W49 and thereafter	EOT
Clinical chemistry	X	X	X	X	X	X	X[2]	X[2]	X	X[2]	X	X
Hematology	X	X	X	X	X	X	X[2]	X[2]	X	X[2]	X	X
Liver chemistry	X	X	X	X	X	X	X[2]	X[2]	X	X[2]	X	X
Troponin, N-terminal pro–B-Type natriuretic peptide (NT-proBNP)	X	X	X	X	X	X			X		X	X
Coagulation	X	X	X	X	X	X	X[2]	X[2]	X	X[2]	X	X
Factor VII Assay[1]	X			X		X						
HbA1c	X					X			X		X	X
Fasting lipids	X					X			X		X	X
Thyroid (Thyroid stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4))[3]	X					X			X		X	X
Pancreatic Markers	X	X	X	X	X	X			X		X	X
Urinalysis	X	X	X	X	X	X			X		X	X
HIV, Hepatitis B surface antigen (HBsAg), Hepatitis C Virus (HCV) Antibody	X											
PSA[2]	X											
Testosterone	X											X

1. In addition to scheduled timepoints, perform if PT or INR or aPTT are ≥1.5XULN, or in case of a bleeding event.
2. **With the implementation of amendment 04, samples for PSA will no longer be collected. Disease assessment should be managed according to local standard of care**
3. TSH testing is mandatory. T4 testing is only required if TSH is abnormal. T3 testing is required when clinically applicable (if both TSH and T4 are abnormal).

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.

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.

Scan data may be transferred and reviewed by an independent cardiologist. Instructions for submission of qualifying scans are provided in the SRM. With the implementation of amendment 04, transfer of scan data for independent cardiologist review is no longer required.

Refer to Section 5.4.3 for LVEF stopping criteria. For management of other changes identified by ECHO or MUGA, see Appendix 2.

7.3.5. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 11, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

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

Some laboratory assessments can vary throughout the day. It is recommended but not mandated that laboratory assessments are collected at approximately the same time on each clinic day.

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

From the first dose of GSK525762 and abiraterone/enzalutamide until 14 days after the last dose of study treatment, all laboratory tests with abnormal values that are considered clinically significant should be repeated as clinically indicated until the values return to normal (per institutional guidelines) or back to the pre-study baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

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,

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.

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

7.3.7. Pregnancy

Details of all pregnancies in female partners of male subjects will be collected after the start of dosing and until at least 16 weeks post-last dose.

If a pregnancy is reported then the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 12.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

7.4. Pharmacokinetics

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

Blood samples for pharmacokinetic (PK) analysis of abiraterone/enzalutamide and GSK525762 (including relevant metabolite(s)) will be collected at the time points indicated in Table 7, Table 8, Table 9, and Table 10. The actual date and time of each blood sample collection will be recorded. Subjects should be instructed to withhold their dose of orally administered study drugs, including GSK525762 and abiraterone/enzalutamide, until after the pre-dose pharmacokinetic blood sample is collected.

The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring. Blood samples for pharmacokinetic analysis should be collected at the time of a SAE whenever possible.

Plasma analysis will be performed under the supervision of GlaxoSmithKline by an external vendor, the details of which will be included in the SRM. Concentrations of GSK525762 (plus any relevant metabolite(s)) and abiraterone/enzalutamide will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Details of PK blood sample collection, processing, storage and shipping procedures are provided in the SRM.

7.5. Pharmacodynamics

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

Tumor samples will be collected pre-dose and on-treatment in order to evaluate changes in molecular markers of BET inhibition (e.g., expression of RNA/proteins regulated by BET) and AR signalling.

7.5.1. Tumor Biopsy Collection/Surgical Procedures

In the dose escalation and expansion cohort(s), paired fresh biopsies must be provided pre- (within 28 days of the first dose) and on-treatment at the time points indicated from all the subjects. Any fresh on-treatment biopsy should be accompanied by a whole blood sample collected as close as possible to the time of biopsy (preferably within 1h). Subjects providing an on-treatment fresh tumor biopsy must have received at least 4 consecutive days of GSK525762 prior to the collection of the sample. Further details regarding sample type and processing will be provided in the SRM. If a potential subject does not have disease amenable to biopsy, participation may occur only upon discussion with and approval of the medical monitor; in this situation, an archival tumor sample retrieved after completion of most recent ADT will be required.

Subjects must have a platelet count of ≥75,000/mm3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy or any other planned surgical procedure. If the on therapy biopsy is not performed during the defined timeline due to lab abnormalities or subject status, it should be performed after subject recovery and the next visit as agreed upon with the medical monitor. Further details regarding sample type and processing will be provided in the SRM.

7.6. Evaluation of Anti-Cancer Activity

With the implementation of amendment 04, CT, MRI, and Bone scan data will no longer be required for disease assessment, and samples for PSA ad CTC-ENU will no longer be collected. See the Time and Events Table (Section 7.1) for the updated schedule of assessments. Disease assessment should be managed according to local standard of care.

The baseline disease assessment will be completed prior to the first dose of GSK525762 and abiraterone/enzalutamide (or first dose of lead in abiraterone/enzalutamide). All imaging to support anti-cancer activity will occur every 8 weeks start of therapy for the first 6 months of treatment and then every 12 weeks thereafter until completion of study treatment. Assessment of PSA will occur every 4 weeks until completion of treatment. Evaluation of CTC will occur at Week 5 and then at Week 9 and every 8 weeks thereafter. All evaluations will occur at the final study visit. See the Time and Events Table (Section 7.1) for the schedule of assessments of anti-cancer activity.

- Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays.
- For post-baseline assessments, a window of 5-7 days is permitted to allow for flexible scheduling (see Section 7.2.2). If the last radiographic assessment was more than 14 days prior to the subject's withdrawal from study and progressive disease has not been documented, a disease assessment should be obtained at the time of withdrawal from study.
- Subjects enrolled with measurable disease by PCWG3-modified RECISIT 1.1 (Appendix 5) and whose disease responds (either CR or PR) should have a confirmatory disease assessment performed no less than 4 weeks after the date of assessment during which the response was demonstrated. The next assessment

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.

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).

Samples will be analyzed at GSK or a laboratory associated with GSK and retained for a maximum of 15 years after the last subject completes the trial.

7.7.3. Circulating Tumor Cells

With the implementation of amendment 04, blood samples for CTC enumeration will no longer be collected.

Blood samples will be collected and analyzed to enumerate CTCs in circulation at the time points indicated in the Time and Events Tables (Section 7.1). The CTCs may also be utilized for additional analysis like alterations in AR genes and may include additional genes implicated in the prostate cancer or related to AR signaling pathway.

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

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

7.7.3.1. CTC Conversion Rate

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

7.7.4. Circulating-Free Tumor DNA/RNA and Soluble Markers

With the implementation of amendment 04, blood samples for cfDNA and soluble markers will no longer be collected.

Tumor-specific cfDNA levels detected in plasma or serum have been found to correlate with increasing tumor burden and decline following therapy. Furthermore, cfDNA in cancer subjects can harbor many genetic alterations (mutations, microsatellite alterations, aberrant methylation), which are generally consistent with the tumor. Thus, tumor-specific circulating cfDNA has the potential to be a useful biomarker of therapeutic response as well as offering a less invasive blood based technique for identifying predictive biomarkers. Additionally exosomes, released from tumors cells into circulation, contain both DNA and RNA; therefore, exosomes may serve as an additional source of predictive biomarkers or facilitate enrichment thereof.

Plasma samples for analysis of cfDNA/RNA and soluble markers will be collected at the time points provided in the Time and Events Tables in Section 7.1.

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

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

7.8. Genetics

With the implementation of amendment 04, if a subject has consented for PGx research but the sample has yet to be collected, this will no longer be required.

An important objective of the clinical study is PGx research. Participation in PGx is optional but all subjects who are eligible for the clinical study will be given the opportunity to participate. Subjects may decline participation without effect on their medical care or care during the clinical study. A separate consent signature is required for PGx research.

Subjects who provide consent will have a blood sample taken for analysis. The presence/absence of genetic variations in host DNA from blood will be analyzed to determine their relationship with response (safety, tolerability, pharmacokinetics, and efficacy) to treatment with GSK525762 and abiraterone/enzalutamide.

7.9. Value Evidence and Outcomes

7.9.1. PRO-CTCAE

With the implementation of amendment 04, the PRO-CTCAE will no longer be completed.

Select items of the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Item Library (version 1.0) will be administered to select subjects based on the availability of translated versions.

7.9.2. EORTC-QLQ-C30, EORTC-QLQ-PR25 & Brief Pain Inventory – Short Form (BPI-SF)

With the implementation of amendment 04, the quality of life questionnaires will no longer be completed.

The effect of GSK525762 and abiraterone/enzalutamide, when given in combination, on symptoms and quality of life will be assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life questionnaire, the EORTC-QLQ-PR25, for evaluating prostate cancer, and the Brief Pain Inventory-Short Form (BPI-SF). These quality of life tools will be assessed as scheduled in Section 7.1.

8. DATA MANAGEMENT

For this study, subject data will be entered into GSK defined eCRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.

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.

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.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

Up to 60 subjects will be enrolled/randomized into each combination arms (based on prior therapy) with up to 30 at each DL to collect safety/tolerability, PK, PD, and clinical activity data. Additional subjects may be enrolled at, or below the combination doses, in order to collect additional safety and PK data.

To determine the maximum sample size for each dose level in dose expansion cohort, Bayesian predictive adaptive design will be used for testing hypotheses and sample size determination:

H_0: RR≤10%

H_A: RR≥30%

Enrollment into specific cohorts may be halted early based on results from interim analyses incorporating emerging response data. Response data from a minimum of 10 evaluable subjects will be required in a cohort before it may discontinue enrollment for futility. Data from evaluable subjects treated in the dose escalation cohorts will be analyzed together with expansion cohort subjects treated at the same dose in the same combination for futility analysis.

Simulation studies were conducted to evaluate the performance of the Bayesian design using utility function defined in Section 9.1.2 under various assumptions for the distribution of true RR and DLT rates across the cohorts. Operating characteristics including power, type I error, estimation of the RR, and the probability of halting enrollment at interim analyses were assessed.

When the treatment effect is positive, the design maintains at least 80% power and type I error rate ≤0.10 on individual cohort. If both dose level are positive, the chance of advancing to phase 2 is as high as 90%. For more details, please see Section 9.4.6.

9.2.2. Sample Size Sensitivity

Sample size sensitivity assessments are described in the simulations presented in Section 9.4.6.

9.2.3. Sample Size Re-estimation or Adjustment

Sample size re-estimation is not planned for this study.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

The **All Treated Population** is defined as all subjects who receive at least one dose of GSK525762 or abiraterone or enzalutamide. Safety and anti-cancer activity will be evaluated based on this analysis population.

The **Modified All Treated Population** is defined as all subjects who receive at least one dose of GSK525762 plus abiraterone/enzalutamide. Safety and anti-cancer activity will be evaluated based on this analysis population if different from the All Treated Population.

All Evaluable Subjects will be defined as the study population used for decision-making at the interim futility analysis. Subjects who have had Week 12 or later visit disease assessment results or have progressed according to the guidelines described in Section 7.6.1 or died or permanently withdrew from the study treatment will be included in this population.

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

Additional analysis populations may be defined in the Reporting and Analysis Plan (RAP)

9.3.2. Interim Analysis

9.3.2.1. Dose Escalation and Safety Analyses

Once 3 to6 subjects have been enrolled at each dose level, an interim analysis will be performed to determine if dose-escalation and/or dose expansion is appropriate. The primary driver for the dose escalation decisions will be safety and tolerability of each dose level cohort.

9.3.2.2. Dose expansion Cohorts

9.3.2.2.1. Efficacy Analyses

Interim analyses during dose expansion cohorts

Interim analysis will be conducted for each DL separately. Interim data will be evaluated to monitor efficacy and safety, and a planned interim analysis may be performed when at least 10 evaluable subjects are available at any DL. Enrollment may be stopped early in any of the expansion cohorts for toxicity or lack of efficacy, should various criteria occur based on accrued data. The decision to stop enrolment within a cohort for futility will be based on the totality of the data including safety/tolerability and evaluation of primary and secondary efficacy endpoints.

9.3.3. Final Analysis

The final analyses will be conducted when the study is completed. Data from the dose escalation and expansion cohort will be combined as appropriate.

9.4. Key Elements of Analysis Plan

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

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

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

For the PFS endpoint, subjects who are alive and have not progressed at the time of analysis will be censored at the date associated with the last visit with adequate assessment.

Demographic and baseline characteristics will be summarized.

9.4.1. Safety Analyses

Safety data for this study be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

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

9.4.1.1. Extent of Exposure

Extent of exposure of GSK525762 and abiraterone or enzalutamide will depend on tolerability of the subjects to the doses administered and the course of their disease. The number of subjects exposed to the combination of GSK525762 and abiraterone or enzalutamide will be summarized for each dose level administered.

9.4.1.2. Adverse Events

Adverse events (AEs) will be coded using the standard MedDRA and grouped by system organ class. Adverse events (AEs) will be graded by the investigator according to the NCI-CTCAE v4 [NCI-CTCAE, 2009].

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

Dose-limiting toxicities (DLTs) will be listed for dose escalation subjects and summarized by dose cohort.

Any AEs of special interest will be summarized as detailed in the RAP.

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

9.4.1.3. Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized using frequencies and proportions according to NCI-CTCAE v4. Laboratory test results outside the reference ranges that do not have an associated NCI-CTCAE criterion will be summarized using proportions. Summaries by visit will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied). Unscheduled data will be included in ‘worse case post baseline’ summaries which will capture a worst case across all scheduled and unscheduled visits after the first dose of study treatment. Further details will be provided in the RAP.

9.4.1.4. Other Safety Measures

Data for vital signs, ECGs, and ECHOs and/or MUGA scans will be summarized based on predetermined criteria identified to be of potential clinical concern. Further details will be provided in the RAP.

9.4.2. Pharmacokinetic Analyses

9.4.2.1. Pharmacokinetic Parameters

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling and Simulation (CPMS) Department, GSK.

Pharmacokinetic (PK) analysis of GSK525762 (and its metabolite[s]), and abiraterone concentration-time data will be conducted by non-compartmental methods under the direction of CPMS, Quantitative Sciences, GSK. Calculations will be based on the actual sampling times recorded during the study. The following PK parameters will be determined if data permit:

- maximum observed plasma concentration (Cmax)
- time to Cmax (tmax)
- area under the curve over a dosing interval (AUC(0-τ))
- trough concentration (Cτ)

Sparse plasma concentration-time data for GSK525762 and its metabolite(s) may be combined with data from other studies and analyzed using a population approach. A nonlinear mixed effects model will be used to determine population pharmacokinetic parameters and identify important covariates (e.g., age, weight, or disease related covariates).

9.4.2.2. Statistical Analysis of Pharmacokinetic Data

Statistical analyses of the PK parameters data will be the responsibility of Clinical Statistics, GSK.

GSK525762 and abiraterone or enzalutamide concentration-time data will be listed for each subject and summarized by descriptive statistics at each time point by cohort. Individual subject parameter values as well as a descriptive summary (mean, standard deviation, median, minimum, maximum, and the standard deviation and geometric mean of log-transformed parameters) by dose cohort will be reported.

Data from this study for GSK525762 may be combined with data from others studies for further evaluation of the population PK of GSK525762. Detail of the analysis may be provided in the separate data analysis plan (DAP).

9.4.3. Pharmacokinetic/Pharmacodynamic Analyses

Observed or predicted concentrations will be combined with safety, efficacy, and other pharmacodynamic measures of interest to examine potential exposure response relationships.

Other quantitative safety parameters and biomarkers of interest will be plotted graphically against summary exposure measures (e.g., Cmax, Cτ, and Cav). Where evidence of a signal is seen, linear and non-linear mixed effect models will be fitted to the data to estimate PKPD parameters of interest; slope, baseline (E0), concentration for 50% of maximum effect (EC50) and maximum effect (Emax).

Overall efficacy data, as assessed by PCWG3 criteria may be described using ordered categorical model and/or continuous models with summary exposure parameters (e.g.; Cmax, Ctrough, and Cav) as covariates derived from the population PK analysis. Further model details will be provided in the RAP.

9.4.4. Efficacy Analyses

The clinical activity primary response rate (RR) will be defined as the rate of achieving the following responses

PSA reduction from baseline ≥50% at 12 weeks and/or thereafter

RR

RR is defined as the response rate that a PSA reduction from baseline ≥50% is observed at 12th weeks and later (must be confirmed by a second value). RR will be reported for each cohort along with the exact 95% confidence interval. Waterfall plots will be presented (as per PCWG3 recommendations) that show the maximum percentage of change in PSA from baseline.

The following secondary responses will also be considered for drawing conclusions on the clinical activity of the combination(s):

Disease Control Rate at 24 weeks

Disease control rate (DCR) is defined as the percentage of subjects with SD, PR or CR at ≥ 24 weeks. Subjects with unknown or missing response will be treated as non-responders (i.e. these subjects will be included in the denominator when calculating the percentage).

Duration of PSA response

Duration of PSA response is calculated from the time the PSA value first declines by at least 50% of the Week 1 Day 1 (baseline) value (must be confirmed by a second value) until the time there is an increase of 25% of PSA nadir, provided the absolute increase is at least 2 ng/mL. The increase must be confirmed by a second consecutive measurement that is at least 25% above the nadir. If the PSA never shows a 25% increase over the nadir value, then the patient will be censored at the last PSA measurement. Duration of PSA response will be summarised by the median and presented along its 95% confidence interval.

ORR

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

CTC Response

CTC response rate is defined as the proportion of subjects with a CTC conversion to <5/7.5 mL blood at nadir (confirmed by a second consecutive value obtained four or more weeks later) will be presented along an exact two-sided 95% confidence interval. Subjects with CTC<5/7.5 mL at baseline will be excluded from this analysis. Waterfall plots of maximum CTC falls will also be presented that show the percentage change in CTC counts from baseline. The CTC response need to be confirmed by a second consecutive value obtained four or more weeks later.

Composite Response Rate

CRR is a composite endpoint based on the following – a) response based on PCWG3-modified RECIST 1.1, b) PSA decrease of ≥50% at Week 12 or thereafter, or c) CTC count conversion. The responders for each endpoint are the same as defined in PSA responses, CTC response and CR or PR per PCWG3-modified RECIST 1.1. Subjects with unconfirmed response per PCWG3-modified RECIST 1.1will be classified as non-responders.

The PR and ORR differences of the same Arm between two doses will be provided along with corresponding 95% CI. A chi-square test will be used to test for differences between doses at the final analysis.

Time to disease progression
Time to disease progression is defined as time from first dose date of study treatment to disease progression defined as one or more of the following criteria:

- Radiographic progression 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 without disease progression at the time of analysis will be censored at the earlier date of last PSA assessment and last radiological assessment.

PSA Week 4 response rate
PSA Week 4 response rate (Week 4 RR) is defined as the response rate that a PSA reduction from baseline ≥30% is observed at 4 weeks [Rescigno, 2016]. Week4 RR will be reported for each cohort along with the exact 95% confidence interval. The percentage of subjects have PSA >=25% increase from baseline at 4 weeks will also be reported for each cohort.

Radiographic Progression-free survival (rPFS) will be defined as the time from study treatment start until the first date of either disease progression or death due to any cause. The date of disease progression will be defined as the earliest date of disease progression as assessed by the investigator using PCWG3-modified RECIST, version 1.1 or

progression on bone scan. For subjects who have not progressed or died at the time of the rPFS analysis, censoring will be performed using the date of the last adequate disease assessment. In addition, subjects with an extended loss to follow-up or who start a new anti-cancer therapy prior to a rPFS event will be censored at the date of the last adequate disease assessment (e.g. assessment where visit level response is CR, PR, or stable disease [SD]) prior to the extended loss to follow-up or start of new anti-cancer therapy, respectively. Further details on rules for censoring will be provided in the RAP. rPFS will be summarized by dose level specified in expansion cohort using Kaplan-Meier quantile estimates along with 2-sided 95% CIs at the time of interim and end of Phase I interim analysis, if data warrant.

For the analysis of **overall survival (OS)**, the last date of known contact will be used for those subjects who have not died at the time of analysis; such subjects will be considered censored. Further details on rules for censoring will be provided in the RAP. If data warrant, OS will be summarized by arm and dose level using Kaplan-Meier quantile estimates along with 2-sided 95% CIs.

9.4.5. Other Analyses

9.4.5.1. Translational Research Analyses

The results of translational research investigations will be reported separately from the main clinical study report (CSR). All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Further details on the translational research analyses will be addressed in the RAP.

9.4.5.2. Novel Biomarker(s) Analyses

The results of these biomarker investigations, including correlation between ESR1 mutations and clinical response, will be reported separately from the main clinical study report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Additional exploratory analyses may be performed to further characterize the novel biomarker.

9.4.5.3. Pharmacogenetic Analyses

Further details on pharmacogenetic (PGx) analyses will be addressed in Appendix 9 and the PGx RAP.

9.4.6. Simulations and Design Operating Characteristics

9.4.6.1. Simulation Description

Extensive simulations have been conducted to develop and understand the performance of the seamless design, interim monitoring, and decision criteria. The simulations are conducted for one combination arm. Same operating characteristics are expected in the other combination arm.

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.

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 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.

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:

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

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

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

GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.

If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.

If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.

If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.

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

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

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

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

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ACLS	Advance Cardiac Life Support
ADT	Androgen-deprivation therapy
AE	Adverse event
AkT	Protein kinase B
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AR	Androgen receptor
AR-V	Androgen receptor splice variants
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
AUC(0-τ)	Area under the curve over a dosing interval
BAL	Brochoalveolar lavage
BCRP	Breast Cancer Resistance Protein
BET	Bromodomain and extraterminal domains
BID	*Bis in die* - Twice daily
BPI- SF	Brief Pain Inventory-Short Form
BRD	Bromodomain
Cav	Average observed concentration
CBC	Complete blood count
cfDNA	Cell free deoxyribonucleic acid
CI	Confidence interval
Cmax	Maximum observed concentration
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacology Modeling and Simulation
CR	Complete response
CRR	Composite response rate
CRPC	Castrate-resistant prostate cancer
CSMU	Clinically significant minimum utility
CSR	Clinical study report
CT	Computerized Tomography
CTC	Circulating tumor cells
CTC – ARV	CTC measuring AR-Vs
CTC – ENU	CTC enumeration
CV	Cardiovascular or Coefficient of variance
CYP	Cytochrome P450
Cτ	Pre-dose (trough) concentration at the end of a dosing interval

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

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

NE	Not evaluable
NSAIDs	Non-steroidal anti-inflammatory drugs
NT-proBNP	N-terminal pro–B-Type natriuretic peptide
NYHA	New York Heart Association
OAT	Organic anion transporter
ORR	Objective response rate
OS	Overall survival
PARP	Poly ADP ribose polymerase
PCR	Polymerase chain reaction
PCWG3	Prostate cancer working group 3
PD	Pharmacodynamic or Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PGx	Pharmacogenetics
Pgp	P-glycoprotein
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetics
PR	Partial response
PRES	Posterior Reversible Encephalopathy Syndrome
PRO-CTCAE	Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events
PSA	Prostate-specific antigen
PSA50	Prostate-specific antigen from baseline ≥50%
PT	Prothrombin time/ Preferred (coded) term
PTEN	Phosphatase and tensin homolog
PTT	Partial thromboplastin time
QD	*quaque die* - Once daily
qRT-PCR	Quantitative reverse transcription polymerase chain reaction
QTc	Corrected QT interval
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended Phase II dose
rPFS	Radiological progression free survival
RNA	Ribonucleic acid
RR	Response rate
SAE	Serious adverse event
SCR	Screening visit
SD	Stable disease
SRM	Study Reference Manual
SRT	Safety review team
TID	*ter in die* – three times daily
Tmax	Time to maximum concentration
TSH	Thyroid stimulating hormone
TTG	Time to tumor growth
T3	Free triiodothyronine

T4	Free thyroxine
ULN	Upper limit of normal
US	United States
W	Week
Wnt	Wingless-type MMTV integration site family member

Trademark Information

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12.2. Appendix 2: Management of Suspected Toxicity

The following dose modification criteria in Table 13 should be used to provide guidance, but not act as a replacement for sound clinical judgment. If a given toxicity is considered by the investigator to be related to a single investigational drug and not both, then dose modification may only occur with the drug associated with a specific toxicity or event of clinical concern.

Table 13 Dose Adjustment/Stopping Safety Criteria

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Thrombocytopenia	Grade 1 (platelets <LLN to ≥75,000/mm^3) & Grade 2 (platelets <75,000 to ≥50,000/mm^3)	Continue dosing at same dose level with weekly or more frequent monitoring as necessary.
	Grade 3 (platelets <50,000, ≥25,000/mm^3)	Withhold GSK525762 and check activated partial thromboplastin time (aPTT), PT, and INR. Monitor CBC and coagulation studies at least twice a week, or more frequently if clinically indicated. Hold GSK525762 until thrombocytopenia has resolved to ≤Grade 2 AND aPTT, PT, and INR are all ≤ ULN. Drug may then be restarted at a dose level lower, after discussion with medical monitor. If safety lab abnormalities recur following rechallenge, drug may be discontinued or restarted at another dose level lower, after discussion with medical monitor. If safety lab abnormalities recur to the same level following a second rechallange, drug will be discontinued.
	Grade 4 (platelets <25,000/mm^3),or any moderate to severe bleeding accompanied by drug related thrombocytopenia	Withhold GSK525762 and check aPTT, PT, and INR. Monitor CBC and coagulation studies every 2-3 days. Hold GSK525762 until thrombocytopenia has resolved to ≤Grade 2 AND aPTT, PT, and INR are all ≤ ULN. Drug may then be restarted at a lower dose level, after discussion with medical monitor. If safety lab abnormalities recur following rechallenge, drug may be discontinued until platelet count recovers to Grade 2 (≥50,000/mm^3). For subjects with moderate to severe bleeding requiring transfusion support, GSK525762 should be permanently discontinued. If platelet count does not recover to ≥50,000/mm^3 (Grade 2) within 14 days, GSK525762 should be permanently discontinued. If platelet count recovers to ≥50,000/mm^3 (Grade 2) within 14 days, GSK525762 may be continued at the

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
		current/reduced dose after discussion with the medical monitor. If platelet count does not recover to ≥25,000/mm^3 (Grade 3) within 7 days, GSK525762 should be permanently discontinued.
QTcF	If ≥ 60 msec change from baseline occurs AND QTcF ≥500 msec OR QTcF≥530 msec AND <60 msec change from baseline (average of three ECGs over at least 15 minutes)	Discontinue GSK525762 and notify the Medical Monitor. • Evaluation by cardiologist • Supplement electrolytes to recommended levels: a. Maintain serum potassium > 4mol/L b. Maintain serum magnesium levels >0.85 mmol/L • Rule out other potential etiologies for prolonged QTcF such as cardiac ischemia • Discontinue any concomitant medications with potential for QTcF prolongation. • 24-hour telemetry monitoring if clinically indicated. This subject may consider restarting study treatment at one dose level reduced if all of the following criteria for QTcF re-challenge are met. In France, if stopping criteria is met, subjects will not be allowed to restart or be rechallenged. If approval for re-challenge is granted, the subject must be re-consented (with a separate informed consent specific to QTc prolongation) (1) QTcF reduced to <480 msec, (2) Potassium and magnesium levels are within institutional normal range, (3) A favorable risk/benefit profile (in the medical judgement of the Investigator and the Medical Monitor), (4) Approval within GSK medical governance: a. agreement with SERM MD and PPL, b. review with Chair or co-Chair of the GSK QT panel, c. SERM VP and Clinical VP approval d. Head Unit Physician approval (5) Institutional IRB (or equivalent) approval, if required by IRB (or equivalent), and (6) The subject is re-consented regarding the possible increased risk of QTc prolongation. Discontinuation procedures: If the subject is withdrawn due to QTcF event, the subject should complete the following activities post-dose: (1) Evaluation by cardiologist. (2) Weekly assessments for QTcF until ≤30 msec change from baseline reached, and then next assessment at 4 weeks post-dose.

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
		(3) If QTcF results have not resolved to baseline by 4 weeks post-dose, then continue every 4-5 weeks until resolution
Troponin	Troponin level >ULN	Contact the subject immediately for evaluation of symptoms and to obtain ECG. Repeat troponin as soon as possible (ideally within 24-48 hours). For asymptomatic subjects with repeat troponin values >ULN, hold study medication(s), refer to a cardiologist and contact the Medical Monitor. If the repeat value is within the normal range, the subject may continue study medication with close follow-up for symptoms, ECG monitoring and further troponin measurements as clinically indicated. If the subject is symptomatic or the troponin level approaches the threshold for MI according to local lab parameters, the study medication must be permanently discontinued and the subject will be referred immediately to a cardiologist for appropriate medical care.
LVEF	• Asymptomatic, absolute decrease of >10% in LVEF compared to baseline and the ejection fraction is below the institution's lower limit of normal (LLN)	• Interrupt investigational drug(s) and repeat evaluation of LVEF within 2 weeks • If LVEF recovers (defined as ≥LLN and absolute decrease ≤10% compared to baseline) at any time during the next 4 weeks, after consultation and approval of the medical monitor, the subject may be restarted on investigational drug(s) at a reduced dose. Monitoring to be performed at 2 and 4 weeks after restarting investigational drug(s) and then per protocol specifications. • If LVEF does not recover within 4 weeks, permanently discontinue investigational drug(s). Evaluation by a cardiologist will be conducted. Ejection fraction should continue to be monitored at 2 weeks, 4 weeks and every 4 weeks until 16 weeks or resolution, whichever is longer.
	• Grade 3 or 4	• Permanently discontinue investigational drug(s). Evaluation by a cardiologist will be conducted. Ejection fraction should be monitored at 2 weeks, 4 weeks and then every 4 weeks until 16 weeks or resolution, whichever is longer.
Liver	• ALT ≥5X ULN, OR • ALT ≥3X ULN plus either bilirubin ≥2X ULN (>35% direct bilirubin, bilirubin fractionation required) or INR	Refer to Section 5.4.1 for liver chemistry stopping criteria and treatment algorithms, and to Appendix 7 for reporting and follow-up of suspected liver events. In France, if stopping criteria is met, subjects will not be allowed to restart or be rechallenged. For subjects who develop hepatotoxicity during treatment,

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
	>1.5 without evidence of biliary obstruction or progressive disease, OR • ALT ≥3X ULN plus symptoms of liver injury or hypersensitivity[a]	hold abiraterone until recovery. Retreatment may be initiated at a reduced dose of 750 mg QD following return of liver function tests to baseline. If hepatotoxicity recurs at dose of 750 mg QD, reduce dose to 500 mg QD following return of liver function tests to baseline. If hepatotoxicity recurs at 500 mg, discontinue treatment with abiraterone.
	• Elevated bilirubin, hypoalbuminemia, prolonged PT, ascites, and/or encephalopathy	Refer to Appendix 11 for definition of Child-Pugh score • Child-Pugh Class A: No change to abiraterone dose required • Child-Pugh Class B: Reduce dose of abiraterone to 250 mg, administered as per the standard schedule. • Child-Pugh Class C: Do not use. In addition, please refer to "other non-hematologic toxicity", below, for management of GSK525762
	• Elevated bilirubin without other evidence of liver injury	Refer to "other non-hematologic toxicity", below
Hypo- and Hyperglycemia (for management purposes, refer to mild, moderate and severe intensity criteria; however for eCRF reporting use NCI-CTCAE v4.0 [NCI-CTCAE, 2009] grading system)	• Fasting blood glucose >150 mg/dL to 250 mg/dL (Mild hyperglycemia)	• Monitor fasting and preprandial glucose. • If persistent over 2 repeats over 3-4 weeks, consult Diabetologist, consider starting metformin
	• Fasting blood glucose any blood glucose >250 mg/dL (Moderate to Severe hyperglycemia)	• Hold investigational product(s) and instruct subject to notify investigator immediately. • Monitor for ketoacidosis as clinically indicated. • If subject has evidence of ketoacidosis, initiate prompt therapy. Antihyperglycemic therapy with insulin is preferred. Consult Diabetologist/Endocrinologist .Careful monitoring should be performed to control for rebound hypoglycemia as effect of investigational product(s) resolve • May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with Medical monitor.
	• Fasting blood glucose <70 mg/dL (Moderate to Severe hypoglycemia)	• Hold investigational product(s) • Provide sugar containing liquids and monitor blood sugar closely. Check for insulin and c-peptide levels. After blood sugar normalizes • Restart study treatment one dose level lower if the hypoglycemia cannot be attributed to any other cause, and fasting blood sugar will be monitored on a daily basis until the blood glucose level is stabilized.

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Diarrhea	• Grade 1	• Initiate supportive care including loperamide.
	• Grade 2	• Initiate supportive care including loperamide. Consider temporary discontinuation of study medications and discuss with Medical Monitor.
	• Grade 3 or 4	• Above plus consider IV hydration, hospital admission and prophylactic antibiotics as appropriate. Withhold study drug until diarrhea has resolved to ≤Grade 1, continue diarrheal prophylaxis. • Restart study treatment one dose level lower.
Mucositis	• Grade 1-2	• Encourage oral hygiene. Offer topical supportive anesthetics. Encourage adequate hydration.
	• Grade 3-4	• (Above plus systemic opiate administration as needed.) Consider IV hydration and hospital admission as appropriate. • For mucositis >Grade 3, hold GSK525762 until mucositis is <Grade 1 and resume the same dose of GSK525762. If mucositis >Grade 3 recurs, hold GSK525762 until mucositis is <Grade 1, then reduce GSK525762 one dose level. If mucositis >Grade 3 recurs a third time at reduced dose, hold GSK525762 until mucositis resolved to <Grade 1, then reduce GSK525762 one dose level (if possible) or discontinue permanently
Pneumonitis	• Grade 1	• (For <u>all</u> Grades) Obtain high resolution chest CT. • Consider evaluation by pulmonologist. Consider room air O_2 saturation at rest via weekly room air pulse oximetry reading (X 2, 5 mins apart). • If any decline is observed in O_2 saturation, hold study drug, repeat chest x-ray to determine if progression of pneumonitis has occurred and consult pulmonologist.
	• Grade 2	• Hold investigational drug(s) until recovery to ≤ Grade 1, then reduce dose by at least 25%. Discontinue investigational drug(s) if no recovery to ≤ Grade 1 within 4 weeks. • Must be evaluated by a pulmonologist. Perform pulmonary function tests including: spirometry, Diffusing Capacity of the Lung for Carbon Monoxide (DLCO), and weekly room air O_2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). Repeat evaluations every 4 weeks until pneumonitis has resolved. Consider a bronchoscopy with biopsy and/or bronchoalveolar lavage. (BAL). • Treat only if symptomatic. Consider corticosteroids if symptoms are troublesome and infectious origin is ruled out. Taper as medically indicated.

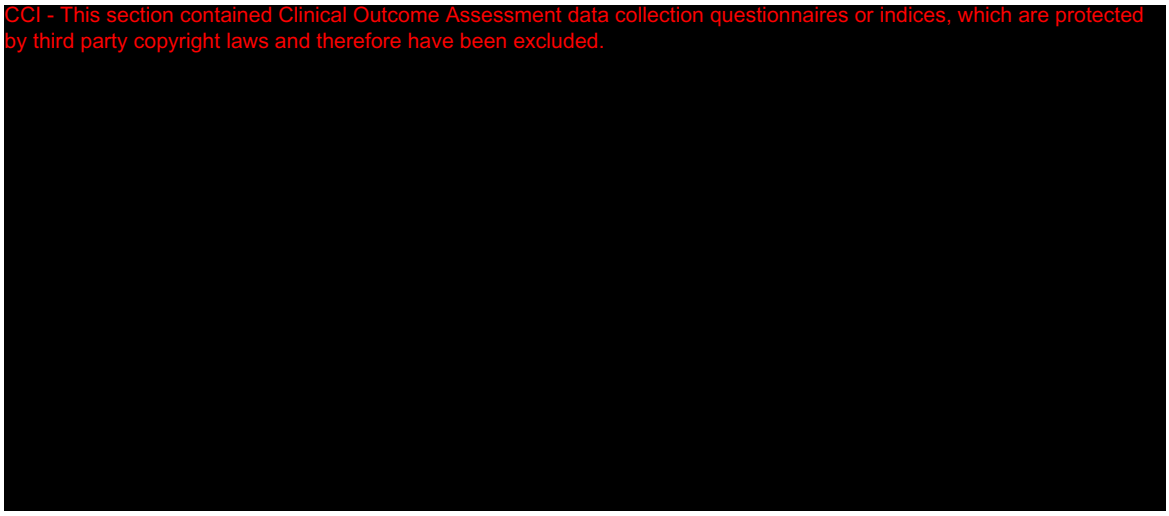
Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
	• Grade 3 and 4	• Discontinue investigational drug(s) • Evaluation by pulmonologist required. • Required pulmonary function tests including: spirometry, DLCO, and weekly room air O_2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). Repeat evaluations at least every 8 weeks until return to normal. Bronchoscopy with biopsy and/or BAL is recommended. • Consider treatment with corticosteroids in the appropriate clinical setting and in consultation with the pulmonologist (1-2 mg/kg of prednisone [or equivalent] IV once daily) if infectious origin is ruled out. Taper over 4-6 weeks.
Other non-hematologic toxicity (except those listed in Section 4.2.2.3)	• Grade 1	• No change in dose
	• Grade 2	• For drug-related Grade 2 toxicities, continue dosing with no change or may consider holding for up to 1 week for toxicity to be < Grade 2. Continue at the same dose (dose reduction is required if the grade 2 toxicity is considered a DLT)
	• Grade 3	• Hold dose until toxicity is ≤Grade 1, then restart with no change for 1st episode. Reduce by one dose level with 2nd episode if recovery to ≤Grade 1 within 21 days. If no recovery to ≤Grade 1 after a 21 day delay in the 2nd episode, subject should be permanently discontinued.
	• Grade 4	• In patients with objective evidence of clinical benefit, hold therapy until toxicity is ≤Grade 1, then restart with one dose level lower. If the same Grade 4 non-hematological toxicity recurs, study drug will be permanently discontinued.
Enzalutamide General Toxicity	• Enzalutamide related Grade 3 or 4	• Withhold dosing for one week or until symptoms improve to ≤ Grade 2, then resume at the same or reduced dose (120 mg or 80 mg), if warranted.

a. 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)

Abbreviations: GSK=GlaxoSmithKline; QTcF= QT duration corrected for heart rate by Fridericia's formula; ECG=Electrocardiogram; IRB=Institutional review board; EC=Ethics committee; ULN=Upper limit of normal; LLN=Lower limit of normal; CV= Coefficient of variance; LVEF= Left ventricular ejection fraction; ALT=Alanine Transferase; BAL=Bronchoalveolar lavage; DLCO=Diffusing Capacity of the Lung for Carbon Monoxide; IL=Interleukin

12.3. Appendix 3: ECOG Performance Status

The performance status assessment is based on the ECOG scale [Oken, 1982]



12.4. Appendix 4: Cockcroft and Gault Method for Calculated Creatinine Clearance

Calculated creatinine clearance (mL/min) **=**	(140 – age [yrs]) × weight (kg)
	72 × serum creatinine (mg/100mL)
Female subjects: multiply by 0.85	

[Cockcroft, 1976]

12.5. Appendix 5: Guidelines for Assessment of Disease, Disease Progression and Response Criteria – modified and adapted from PCWG3 guidelines [Scher, 2016] and RECIST 1.1 [Eisenhauer, 2009]

12.5.1. Baseline Documentation of Target and Non-Target Lesions

- All baseline lesion assessments must be performed within 28 days of randomization.
- Lesions ≥10mm in the longest dimension are considered measurable.
- Lymph nodes that have a short axis of <10mm are considered non-pathological and should not be recorded or followed.
- Lymph nodes with <15mm and but ≥10mm short axis are considered pathologic according to clinical discretion, and nontarget
- Pathological lymph nodes with ≥15mm short axis are considered measurable and can be selected as target lesions.
- Per PCWG3 guidelines, documentation of prior progression should be defined as growth of pre-existing lesions, development of new lesions, or both. Documentation of site of progression either in a single organ or disease site versus multiple sites should occur. Bone scan lesions should be identified and tracked independently.
- Per PCWG3 guidelines, documentation of nodal disease should be considered either loco-regional (pelvic) versus extrapelvic (e.g., retroperitoneal, mediastinal, thoracic, other). Visceral disease (e.g., lung/liver/CNS) should be documented separately from nodal disease. Up to 5 measurable lesions can be documented per site of spread (e.g., nodes, lung, liver as separate sites). Each of these lesions should be identified, recorded and measured at baseline. These lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- Documentation of progression at entry into trial should be recording as PSA alone, bone with or without nodes by location, nodes by location only or viscera (or other sites).

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

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

- Bone scans are standard for PCWG3 guidelines, with documentation of absence or metastasis recorded at baseline.
- All other lesions (or sites of disease) should be identified as non-target and should also be recorded at baseline. Non-target lesions will be group by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

- The following are required at baseline: CT for Chest/Abdomen/Pelvis or MRI for Abdomen/ Pelvis. At each post baseline assessment, evaluations of the sites of disease identified by these scans are required.

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

A baseline brain scan is required for all subjects. For subjects without CNS disease at baseline, subsequent brain scans should only be performed as clinically indicated (e.g. symptoms suggestive of CNS progression).

12.5.2. Assessment Guidelines

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion. Contrast agents must be used in accordance with the Image Acquisition Guidelines.
- All measurements should be taken and recorded in millimeters (mm), using a ruler or calipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.
- Fluorodeoxyglucose (FDG)- Positron emission tomography (PET) is generally not suitable for ongoing assessments of disease. However FDG-PET can be useful in confirming new sites of disease where a positive FDG-PET scans correlates with the new site of disease present on CT/MRI or when a baseline FDG-PET was previously negative for the site of the new lesion. FDG-PET may also be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.
- If PET/CT is performed then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT on the eCRF.

Clinical Examination: Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler/calipers to measure the size of the lesion, is required [Eisenhauer, 2009].

CT and MRI: **Contrast enhanced CT with 5mm contiguous slices is recommended.** Minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimised for

the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible the same scanner should be used [Eisenhauer, 2009].

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

12.5.3. Guidelines for Evaluation of Disease

Measurable and Non-measurable Definitions

Measurable lesion:

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

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

Additionally lymph nodes can be considered pathologically enlarged and measurable if

- ≥15mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5mm). At baseline and follow-up, only the short axis will be measured [Eisenhauer, 2009].

Non-measurable lesion:

All other lesions including lesions too small to be considered measurable (longest diameter <10 mm or pathological lymph nodes with ≥ 10 mm and <15 mm short axis) as well as truly non-measurable lesions, which include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques (Eisenhauer, 2009).

Measurable disease: Measureable lesions are not required at study entry if subject meets PSA requirements for progression (rising PSA values at a minimum of 1-week intervals or PSA doubling time with at least 3 values available ≥4 weeks apart). . Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion.

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

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

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.

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

Evaluation of overall response

Table 14 presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for subjects with measurable disease at baseline.

Table 14 Evaluation of Overall Response for Subjects with Measurable Disease at Baseline

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

CR=complete response, PR = partial response, SD=stable disease, PD=progressive disease, NA= Not applicable, and NE=Not Evaluable

Note:

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

Evaluation of best overall response

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

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after first dose at a minimum interval of 49 days.
- If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PD.

Alternatively, subjects lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

Confirmation Criteria:

- To be assigned a status of PR or CR, a confirmatory disease assessment should be performed no less than 4 weeks (28 days) after the criteria for response are first met.

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

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**

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

1. For the purpose of these guidelines “baseline” refers to laboratory assessments performed closest and prior to first dose of study treatment

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. *Drug Metab Dispos* 2009; 37:1779-1784.

12.7. Appendix 7: Liver Safety – Study Treatment Restart or Rechallenge Guidelines

In France, if stopping criteria is met, subjects will not be allowed to restart or be rechallenged.

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

- GSK Medical Governance approval **is granted** (as described below),
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

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

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

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

Risk factors for a fatal drug rechallenge outcome include:

- hypersensitivity with initial liver injury (e.g. fever, rash, eosinophilia) [Andrade, 2009]
- jaundice or bilirubin >2xULN with initial liver injury (direct bilirubin >35% of total)
- subject currently exhibits severe liver injury defined by: ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total), or INR≥1.5
- serious adverse event or fatality has earlier been observed with drug rechallenges [Papay, 2009]
- evidence of drug-related preclinical liability (e.g. reactive metabolites; mitochondrial impairment [Hunt, 2010])

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

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

- Investigator requests consideration of rechallenge with study treatment for a subject who is receiving compelling benefit with study treatment that exceeds risk, and no effective alternative therapy is available.
- Ethics Committee or Institutional Review Board approval for rechallenge with study treatment must be obtained, as required.
- If the rechallenge is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the rechallenge with study treatment. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for rechallenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If after study treatment rechallenge, subject meets protocol-defined liver chemistry stopping criteria, study treatment should be permanently discontinued.
- Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment rechallenge.
- GSK to be notified of any adverse events, as per Appendix 8.

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

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

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

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

- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.
- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment restart.
- GSK, or designee, to be notified of any adverse events, as per Appendix 8.

References:

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

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

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

12.8. Appendix 8: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.8.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's

condition.

- 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

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

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

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.

12.9. Appendix 9: Genetic Research

Genetics – Background

Naturally occurring genetic variation may contribute to inter-individual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration (AMD) are reported to account for much of the risk for the condition [Gorin, 2012] with certain variants reported to influence treatment response [Chen, 2012]. Thus, knowledge of the genetic etiology of disease may better inform understanding of disease and the development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

Genetic Research Objectives and Analyses

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

- Response to medicine, including GSK525762 and/or abiraterone or enzalutamide, or any concomitant medicines;
- mCRPC susceptibility, severity, and progression and related conditions

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

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

Study Population

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

Study Assessments and Procedures

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

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

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

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

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

Informed Consent

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

Subject Withdrawal from Study

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

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

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

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

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

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

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

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

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

References:

Chen H, Yu KD, Xu GZ. Association between Variant Y402H in Age-Related Macular Degeneration (AMD) Susceptibility Gene CFH and Treatment Response of AMD: A Meta-Analysis. PloS ONE 2012; 7: e42464

Gorin MB. Genetic insights into age-related macular degeneration: Controversies addressing risk, causality, and therapeutics. *Mol. Asp. Med.* 2012; 33: 467-486.

12.10. Appendix 10: Country Specific Requirements

No country-specific requirements exist.

12.11. Appendix 11: Child-Pugh score [Pugh, 1973]

Measure	1 point	2 points	3 points
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.			

Points	Class
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.	

References:

Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973;60:646-649.

12.12. Appendix 12: Contraceptive Guidance and Collection of Pregnancy Information

12.12.1. Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
• **Highly Effective Methods[b] That Have Low User Dependency**
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner   • *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
• **Highly Effective Methods[b] That Are User Dependent**

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  • oral
  • injectable

• Sexual abstinence   • *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

12.12.2. Collection of Pregnancy Information

- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomized to receive study medication.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy
- Female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

12.12.3. References

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12.13. Appendix 13: Protocol Amendment Changes

Protocol changes for Amendment (01-Feb-2017) from Original Protocol (13-Oct-2016)

Protocol Amendment 1 applies to all global site(s) participating in the conduct of the study

Amendment 1 Summary

Amendment 1 includes the following changes which were based on review and comments from the FDA during review: clarifications to Exclusion #6 and addition of new Exclusion Criterion; addition of dose reduction table; additional wording on prohibited and cautionary medications; and adjustments to the Dose Adjustment/Stopping Safety Criteria. In addition to the FDA requests, additional changes which were included were: new information added regarding monotherapy CRPC study; revision to Inclusion #12; clarifications to GSK525762 formulation wording; clarification to planned dose adjustment section; revision to male lifestyle changes with additions of pregnancy section and contraceptive appendix; update of prohibited and cautionary medication tables; various clarifications to Table and Events table; removal of screening CTC-ARV sample; adjustment to timing of CTC-enumeration and exploratory whole blood analysis; adjustment to the visit window wording; clarifications to the laboratory testing section; revision to tumor biopsy section and clarification to analysis population section.

List of Specific Changes

Section 1 - Protocol Synopsis Rationale

Rationale for Change:

Additional wording to clarify results of recently completed analysis for BET115521 monotherapy study – CRPC arm.

Previous text:

Recent studies have shown an alternate mode of AR inhibition by targeting a new class of proteins known as bromodomain and extraterminal domains (BET) [Wyce, 2013]. Studies have demonstrated that BET inhibition can lead to growth arrest and cell death in a variety of preclinical models, including models of CRPC [Wyce, 2013]. An ongoing first-in-human (FIH) study from GlaxoSmithKline (GSK), BET115521, is currently evaluating the safety and preliminary efficacy of single-agent GSK525762, a potent inhibitor of BET proteins, in a number of tumor types including mCRPC.

Revised Text:

Recent studies have shown an alternate mode of AR inhibition by targeting a new class of proteins known as bromodomain and extraterminal domains (BET) [Wyce, 2013]. Studies have demonstrated that BET inhibition can lead to growth arrest and cell death in

a variety of preclinical models, including models of CRPC [Wyce, 2013]. An ongoing first-in-human (FIH) study from GlaxoSmithKline (GSK), BET115521, is currently evaluating the safety and preliminary efficacy of single-agent GSK525762, a potent inhibitor of BET proteins, in a number of tumor types including mCRPC. **Preliminary data from the futility analysis of the CRPC arm indicated there were no partial or complete responses. This data will be further examined as the data continues to mature.**

Section 1 - Protocol Synopsis Overall design

Rationale for Change:

Arm B: Revision of section due to missed wording which is present in the body of the text

Previous text:

However, based on PK analysis from DL80 and DL100 dose escalation cohorts, if the exposure to GSK525762 active moiety is 40% lower than its single agent exposure (determined from GSK525762 80 mg cohort in BET115521 study), DL120 may be opened. The study team will carefully review PK and safety data from the DL80 level to determine if it is acceptable to open the DL120 dose level. If DL120 is opened, subjects in DL120 will begin dosing with GSK525762 at 120 mg and the approved dose of enzalutamide.

Once a higher dose (either DL100 or DL120) and lower dose (DL80) are determined to not exceed the MTD, the dose expansion cohorts at these selected doses will be initiated and will be randomized by prior lines of therapy (L2 or Lx). A total of 30 subjects each will be enrolled into both cohorts, and approximately10 enrolled subjects will be L2 and 20 subjects will be Lx (Figure 2).

Revised text:

However, based on PK analysis from DL80 and DL100 dose escalation cohorts, if the exposure to GSK525762 active moiety is 40% lower than its single agent exposure (determined from GSK525762 80 mg cohort in BET115521 study), DL120 may be opened. The study team will carefully review PK and safety data from the DL80 **and DL100** level**s** to determine if it is acceptable to open the DL120 dose level. If DL120 is opened, subjects in DL120 will begin dosing with GSK525762 at 120 mg and the approved dose of enzalutamide.

Once a higher dose (either DL100 or DL120) and lower dose (DL80) are determined to not exceed the MTD, the dose expansion cohorts at the~~se~~ selected **higher and lower** doses will be initiated and will be randomized by prior lines of therapy (L2 or Lx). A total of 30 subjects each will be enrolled into both cohorts, and approximately10 enrolled subjects will be L2 and 20 subjects will be Lx (Figure 2).

Section 1 - Synopsis Inclusion Criteria

Rationale for Change:

Clarification of Inclusion Criteria #12 with required time frame of contraception use

Previous text:

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

Revised text:

12. Male subject with a female partner of childbearing potential or pregnant must agree to use two acceptable methods of contraception from time of **first dose of study treatment** ~~Screening~~ until **4** ~~3~~ months after the last dose of study treatments.

Section 1 - Synopsis Exclusion Criteria

Rationale for Change:

Due to FDA feedback, the wording related to bleeding was to include clinically significant haemorrhage within a defined time period in addition to known bleeding disorder(s)

Previous text:

6. Subjects with history of known bleeding disorder(s)

Revised text:

6. Subjects with history of known bleeding disorder(s) i**ncluding clinically significant hemorrhage (e.g., GI, neurologic), within the past 6 months.**

Section 1 - Synopsis Exclusion Criteria

Rationale for Change:

Based on FDA review and emerging safety data from the BET115521 monotherapy study, it was suggested that the study limit the use of certain medications. This required a new Exclusion Criteria #8 and caused a re-numbering of criteria after the addition of this new Exclusion Criteria.

New text:

8. Concurrent use of high dose aspirin (doses up to 81mg oral dose daily allowed) 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.

Section 1 - Synopsis Exclusion Criteria

Rationale for Change:

Due to change in Exclusion #6, removed wording to Exclusion #17 to prevent duplication.

Previous text:

17. Subjects with gastrointestinal disorders likely to interfere with absorption of the study medication; History of major gastrointestinal bleeding within the last 6 months.

Revised text:

17. Subjects with gastrointestinal disorders likely to interfere with absorption of the study medication.~~; History of major gastrointestinal bleeding within the last 6 months.~~

Section 2.2 - Brief Background

Rationale for Change:

Additional wording to clarify results of recently completed analysis for BET115521 monotherapy study – CRPC arm.

Previous text:

Recent studies have shown an alternate mode of AR inhibition by targeting a new class of proteins known as BET [Wyce, 2013]. The BET family, comprised of bromodomain 2 (BRD), BRD3, BRD4 and BRDT, recognize acetyl groups on the tails of histones and are critical for recruiting transcriptional machinery necessary for gene expression. BRD4 has been shown to interact with AR, and BET inhibition abrogated BRD4 localization to a subset of AR target loci and reduced AR-mediated gene transcription, causing suppression of AR signaling [Assangani, 2014]. Studies have demonstrated that BET inhibition can lead to growth arrest and cell death in a variety of preclinical models, including models of CRPC [Wyce, 2013]. An ongoing first-in-human (FIH) study from GlaxoSmithKline (GSK), BET115521, is currently evaluating the safety and preliminary efficacy of single-agent GSK525762, a potent inhibitor of BET proteins, in a number of tumor types including mCRPC. Preliminary safety and efficacy data is summarized in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2011N113741_05, 2016].

Revised text:

Recent studies have shown an alternate mode of AR inhibition by targeting a new class of proteins known as BET [Wyce, 2013]. The BET family, comprised of bromodomain 2 (BRD), BRD3, BRD4 and BRDT, recognize acetyl groups on the tails of histones and are critical for recruiting transcriptional machinery necessary for gene expression. BRD4 has been shown to interact with AR, and BET inhibition abrogated BRD4 localization to a

subset of AR target loci and reduced AR-mediated gene transcription, causing suppression of AR signaling [Assangani, 2014]. Studies have demonstrated that BET inhibition can lead to growth arrest and cell death in a variety of preclinical models, including models of CRPC [Wyce, 2013]. An ongoing first-in-human (FIH) study from GlaxoSmithKline (GSK), BET115521, is currently evaluating the safety and preliminary efficacy of single-agent GSK525762, a potent inhibitor of BET proteins, in a number of tumor types including mCRPC. **Preliminary data from the futility analysis of the CRPC arm indicated there were no partial or complete responses. This data will be further examined as the data continues to mature.** Preliminary safety and efficacy data is summarized in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2011N113741_05, 2016].

Section 4.1 – Overall Design

Rationale for Change:

Clarification of wording to clarify selected doses.

Previous text:

Once a higher dose (either DL100 or DL120) and lower dose (DL80) are determined to not exceed the MTD, the dose expansion cohorts at the selected doses will be initiated and will be randomized by prior lines of therapy (L2 or Lx). A total of 30 subjects each will be enrolled into both cohorts, and approximately10 enrolled subjects will be L2 and 20 subjects will be Lx (Figure 4). Refer to Section 4.6 for further dose information.

Revised text:

Once a higher dose (either DL100 or DL120) and lower dose (DL80) are determined to not exceed the MTD, the dose expansion cohorts at the selected **higher and lower** doses will be initiated and will be randomized by prior lines of therapy (L2 or Lx). A total of 30 subjects each will be enrolled into both cohorts, and approximately10 enrolled subjects will be L2 and 20 subjects will be Lx (Figure 4). Refer to Section 4.6 for further dose information.

Section 4.2.2.2 - Dose-Limiting Toxicity

Rationale for Change:

Addition of inadvertently missed superscript footnote letter and update of language of footnote to match DLT in Table 4.

Previous text:

Other	• Inability to receive at least 75% of scheduled doses in the DLT observation period due to drug-related toxicity, or any toxicity which requires permanent discontinuation of investigational agent(s) during the DLT observation period • Grade 2 or higher toxicity that occurs beyond 28 days which in the judgment of the investigator and Medical Monitor is considered to be a DLT

Toxicity Grading based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4 [NCI-CTCAE, 2009]

a. Grade 3 hypertension adequately controlled by antihypertensive medication(s) is not considered to be a DLT.

b. Subjects unable to receive at least 80% of scheduled doses for reasons other than toxicity (e.g., acute illness, disease progression) will not be evaluable for DLT purposes and will be replaced in the cohort.

Revised Text:

Other	• Inability to receive at least 75% of scheduled doses in the DLT observation period due to drug-related toxicity, or any toxicity which requires permanent discontinuation of investigational agent(s) during the DLT observation period[b] • Grade 2 or higher toxicity that occurs beyond 28 days which in the judgment of the investigator and Medical Monitor is considered to be a DLT

Toxicity Grading based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4 [NCI-CTCAE, 2009]

a. Grade 3 hypertension adequately controlled by antihypertensive medication(s) is not considered to be a DLT.

b. Subjects unable to receive at least **75**% of scheduled doses for reasons other than toxicity (e.g., acute illness, disease progression) will not be evaluable for DLT purposes and will be replaced in the cohort.

Section 4.6.2 – Starting Doses

Rationale for Change:

Emerging data from clinical pharmacology to provide updated wording on potential effect of Enzalutamide on the starting dose of GSK525762 in combination

Previous text:

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%, as predicted by a mechanistic physiologically based pharmacokinetic (PBPK) model, as part of the

SimCYP population-based PBPK simulator incorporating the effects observed on GSK525762 and active metabolites exposures following co-administration with itraconazole. Therefore, the initial dose of GSK525762 in both arms should be approximately equivalent.

Revised text:

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)**. ~~, as predicted by a mechanistic physiologically based pharmacokinetic (PBPK) model, as part of the SimCYP population-based PBPK simulator incorporating the effects observed on GSK525762 and active metabolites exposures following co-administration with itraconazole~~ Therefore, the initial dose of GSK525762 in both arms should be approximately equivalent.

Section 4.6.4.1 – Cardiovascular Safety Findings

Rationale for Change:

Removed wording which should have been removed in original protocol.

Previous wording:

To monitor for cardiomyopathy and valvular toxicity, echocardiograms will be performed at the time points specified in the Time and Events tables (Section 7.1). Management guidelines (Appendix 2) and stopping criteria (Section 5.4.2 and Section 5.4.3) are incorporated in the protocol.

Revised wording:

To monitor for cardiomyopathy~~and valvular toxicity~~, echocardiograms will be performed at the time points specified in the Time and Events tables (Section 7.1). Management guidelines (Appendix 2) and stopping criteria (Section 5.4.2 and Section 5.4.3) are incorporated in the protocol.

Section 5.1 - Inclusion Criteria

Rationale for Change:

Clarification of Inclusion Criteria #12 with required time frame of contraception use

Previous text:

12. Male subject with a female partner of childbearing potential or pregnant must agree to use two acceptable methods of contraception from time of Screening until 3 months after the last dose of study treatments (Section 6.10.2).

Revised text:

12. Male subject with a female partner of childbearing potential or pregnant must agree to use two acceptable methods of contraception from time of **first dose of study treatment** ~~Screening~~ until **4** ~~3~~ months after the last dose of study treatments (Section 6.10.2).

Section 5.2 - Exclusion Criteria

Rationale for Change:

Due to FDA feedback, the wording related to bleeding was to include clinically significant haemorrhage within a defined time period in addition to known bleeding disorder(s)

Previous text:

6. Subjects with history of known bleeding disorder(s)

Revised text:

6. Subjects with history of known bleeding disorder(s) i**ncluding clinically significant hemorrhage (e.g., GI, neurologic), within the past 6 months.**

Section 5.2 - Exclusion Criteria

Rationale for Change:

Based on FDA review and emerging safety data from the BET115521 monotherapy study, it was suggested that the study limit the use of certain medications. This required a new Exclusion Criteria #8 and caused a re-numbering of criteria after the addition of this new Exclusion Criteria.

New text:

8. Concurrent use of high dose aspirin (doses up to 81mg oral dose daily allowed) 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.

Section 5.2 - Exclusion Criteria

Rationale for Change:

Due to change in Exclusion #6, removed wording to Exclusion #17 to prevent duplication.

Previous text:

17. Subjects with gastrointestinal disorders likely to interfere with absorption of the study medication; History of major gastrointestinal bleeding within the last 6 months.

Revised text:

17. Subjects with gastrointestinal disorders likely to interfere with absorption of the study medication.~~; History of major gastrointestinal bleeding within the last 6 months.~~

Section 5.3 – Screening/Baseline/Run-in Failures

Rationale for Change:

Wording added to further clarify how subjects would be classified if withdrawn during the combination run-in.

Previous text:

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (Appendix 8).

Revised text:

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (Appendix 8). **Run-in failures are defined as subjects who start the run-in of either abiraterone or enzalutamide and withdraw from this run-in and do not proceed to dose with GSK525762.**

Section 6.1 – Investigational Product and Other Study Treatment

Rationale for Change:

Clarification of the GSK525762 dosages.

Previous text:

Investigational Product					
Product name:	GSK525762 Besylate Tablets			Abiraterone acetate	Enzalutamide
Unit dose strength(s)/Dosage level(s):	5 mg	20 mg	25 mg	250 mg	40 mg
Dosage form	Tablet	Tablet	Tablet	Tablet	Tablet
Manufacturer	GSK	GSK	GSK	Janssen	Astellas
Physical description:	White to slightly colored, round, biconvex tablets with no markings, film-coated tablet			White to off-white, oval tablets debossed with AA250 on one side	White to off-white oblong soft gelatin capsules imprinted in black ink with ENZ
Route/ Administration/ Duration:	**Oral;** see Time and Event Tables for schedule and administration timings			**Oral;** see Time and Event Tables for schedule and administration timings	**Oral;** see Time and Event Tables for schedule and administration timings
Dosing instructions:	Dose with 240 mL water and should be taken around the same time every day without regards to timing of meal (If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.)			Dose with 240 mL water and should be taken on an empty stomach, and no food should be consumed from 2hrs before the dose until 1hr after the dose.	Dose with 240 mL water and should be taken around the same time every day without regards to timing of meal (If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.)

NOTE: These formulation details are current at the time of protocol finalization and may be updated in other documents (e.g., SRM and/or informed consent form) without requiring protocol amendment

Revised text:

Investigational Product					
Product name:	GSK525762 Besylate Tablets			Abiraterone acetate	Enzalutamide
Unit dose strength(s)/Dosage level(s):	5 mg [a]	2~~5~~0 mg [a]	**20~~5~~** mg [a]	250 mg	40 mg
Dosage form	Tablet	Tablet	Tablet	Tablet	Tablet
Manufacturer	GSK	GSK	GSK	Janssen	Astellas
Physical description:	White to slightly colored, round, biconvex tablets with no markings, film-coated tablet		**Beige, round, biconvex tablets with no markings, film-coated**	White to off-white, oval tablets debossed with AA250 on one side	White to off-white oblong soft gelatin capsules imprinted in black ink with ENZ
Route/ Administration/ Duration:	**Oral;** see Time and Event Tables for schedule and administration timings			**Oral;** see Time and Event Tables for schedule and administration timings	**Oral;** see Time and Event Tables for schedule and administration timings
Dosing instructions:	Dose with 240 mL water and should be taken around the same time every day without regards to timing of meal (If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.)			Dose with 240 mL water and should be taken on an empty stomach, and no food should be consumed from 2hrs before the dose until 1hr after the dose. **Dose 5 mg prednisone orally twice daily as per prescribing information.**	Dose with 240 mL water and should be taken around the same time every day without regards to timing of meal (If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.)

NOTE: These formulation details are current at the time of protocol finalization and may be updated in other documents (e.g., SRM and/or informed consent form) without requiring protocol amendment

a. The 20 mg tablet formulation is in development and will be utilized during the planned duration of the study. The 5 mg and 25 mg tablet formulation may be discontinued when the 20 mg tablet formulation is available. The use of 20 mg tablets will require regulatory authority approvals.

Section 6.3 – Planned Dose Adjustments

Rationale for Change:

Per FDA response, GSK525762 dose level reductions discussed in the protocol were not well defined. Addition of a dose level reduction table to clarify the possible dose reductions. Additional clarifications were added beyond the FDA response to further clarify dosing of combination product during any GSK525762 dose interruption.

Previous text:

There are no pre-planned dose adjustments per protocol. Dose reductions for individual subjects may be required, based on toxicity observed during the study (please refer to Appendix 2), and the frequency and duration of dose reductions will be reported.

If enzalutamide is discontinued for more than or equal to 7 days, then the maximum dose of GSK525762 should be the single agent RP2D of 80 mg. If enzalutamide is re-started, GSK525762 should remain at 80 mg until after at least 14 days until the dose is escalated, if applicable. Subjects who require permanent discontinuation of either abiraterone or enzalutamide in the combination may continue GSK525762 as a single agent if there is evidence of continuing benefit on treatment. If GSK525762 is continued as a single agent, the maximum dose would be 80 mg. Intra-subject dose escalations from the planned starting dose during dose escalation will not be permitted. Intra-subject dose escalation may be permitted during dose expansion for the lower dose level only if that dose is determined to be futile.

Revised text:

There are no pre-planned dose adjustments per protocol. Dose reductions for individual subjects may be required, based on toxicity observed during the study (please refer to Appendix 2), and the frequency and duration of dose reductions will be reported. **Table 6 clarifies the dose reductions for GSK525762 at any planned study dose.**

Table 6 GSK525762 Dose Reductions

Current GSK525762 Dose:	If subject requires dose level reduction:
40mg	No further dose reduction allowed
60mg	40mg
80mg	60mg
100mg	80mg
120mg	100mg

If enzalutamide is discontinued for more than or equal to 7 days, then **the dose of GSK525762 should be reduced one dose level and** the maximum dose of GSK525762 should be the single agent RP2D of 80 mg. If enzalutamide is re-started, GSK525762 should remain at **the reduced dose level or the maximum single agent RP2D of** 80 mg until after at least 14 days until the dose is escalated, if applicable. Subjects who require permanent discontinuation of either abiraterone or enzalutamide in the combination may continue GSK525762 as a single agent if there is evidence of continuing benefit on treatment. If GSK525762 is continued as a single agent, the maximum dose would be 80 mg. Intra-subject dose escalations from the planned starting dose during dose escalation will not be permitted. Intra-subject dose escalation may be permitted during dose expansion for the lower dose level only if that dose is determined to be futile.

During any dose interruption of GSK525762, abiraterone or enzalutamide may be continued at the protocol dose unless dose interruption of these combination

products is also required. If GSK525762 is permanently discontinued, subject must be discontinued from the treatment and withdrawn from the study.

Section 6.5 – Packaging and Labeling

Rationale for Change:

Added clarification on sourcing of prednisone which is required for abiraterone dosing per the prescribing information.

Previous text:

GSK525762 and abiraterone/enzalutamide will be provided to the sites by GSK. The contents of the labels will be in accordance with all applicable regulatory requirements.

Revised text:

GSK525762 and abiraterone/enzalutamide will be provided to the sites by GSK. **Prednisone will not be supplied by GSK.** The contents of the labels will be in accordance with all applicable regulatory requirements.

Section 6.10.2 – Male Subjects

Rationale for Change:

Protocol template revised allowed contraception for subjects and also moved these choices to an Appendix. Language updated to reflect template update. Additional clarification added to section to confirm non-allowed contraception and restrictions if female partner was to become pregnant during the trial.

Previous text:

Subjects with female partners of child-bearing potential must use one of the following contraceptive methods after the first dose of study treatment and until 16 weeks after the last dose of study drug (note that these requirements do not apply if female partners are not of child-bearing potential):

- Abstinence, defined as sexual inactivity consistent with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception), **OR**
- Condom **PLUS**
- history of surgical sterilization (i.e., vasectomy) with subsequent documentation of azoospermia, **OR**

partner use of a highly effective contraceptive (i.e., a failure rate ≤1%) such as hormonal contraception, intrauterine device, or occlusive cap (diaphragm or cervical/vault cap) plus spermicidal agent (foam/gel/film/cream/suppository).

Revised text:

Subjects with female partners of child-bearing potential must use acceptable, highly effective forms of contraceptive methods (i.e., a failure rate of ≤1%) defined in Appendix 12 ~~one of the following contraceptive methods~~**after the first dose of study treatment and until** ~~16 weeks~~ **4 months after the last dose of study drug (note that these requirements do not apply if female partners are not of child-bearing potential).**

- ~~Abstinence, defined as sexual inactivity consistent with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception),~~ **~~OR~~**
- ~~Condom~~ **~~PLUS~~**
- ~~history of surgical sterilization (i.e., vasectomy) with subsequent documentation of azoospermia,~~ **~~OR~~**

Female partner use of hormonal means of birth control such as oral contraceptives are NOT acceptable forms of birth control given that their efficacy has not been evaluated when given in combination with the investigational drugs.

In addition, male subjects whose partners are or become pregnant while on study medication must continue to use condoms for 4 months after stopping study medications.

Section 6.11.2.1 – Prohibited Medications

Rationale for Change:

Based on FDA review and emerging safety data from the BET115521 monotherapy study, it was suggested that the study limit the use of certain medications. Revision of Table 7 to provide updated list of Prohibited Medication from May 2016 and addition of footnote to Table.

New text:

Subjects may continue to use Aspirin, but doses are not allowed to be greater than 81mg per day. The use of non-steroidal anti-inflammatory drugs (NSAIDs) will be excluded, except for when NSAIDs will provide benefit over other analgesics and then to be used with caution including concomitant use of proton pump inhibitors.

Previous text:

Drugs with a Risk of Torsades de Pointes that are Prohibited

Amiodarone	Donepezil	Methadone
Anagrelide	Dronedarone	Moxifloxacin
Astemizole	Droperidol	Papaverine
Azithromycin	Erythromycin	Pentamidine
Bepridil	Escitalopram	Pimozide
Chloroquine	Flecainide	Probucol
Chlorpromazine	Fluconazole	Procainamide
Cilostazol	Gatifloxacin	Propofol
Ciprofloxacin	Grepafloxacin	Quinidine
Cisapride	Halofantrine	Sevoflurane
Citalopram	Haloperidol	Sotalol
Clarithromycin	Ibutilide	Sparfloxacin
Cocaine	Levofloxacin	Sulpiride
Disopyramide	Levomepromazine	Terfenadine
Dofetilide	Levomethadyl	Thioridazine
Domperidone	Mesoridazine	

Data Source: crediblemeds.org revision date 17 Dec 2015.

Revised text:

Drugs with a Risk of Torsades de Pointes that are Prohibited

Amiodarone	Dronedarone	Moxifloxacin
Anagrelide	Droperidol	Papaverine
Azithromycin	Erythromycin	Pentamidine
Chloroquine	Escitalopram	Pimozide
Chlorpromazine	Flecainide	Procainamide
Cilostazol	Fluconazole	Propofol
Ciprofloxacin	Halofantrine	Quinidine
Citalopram	Haloperidol	Roxithromycin
Clarithromycin	Ibogaine	Sevoflurane
Cocaine	Ibutilide	Sotalol
Disopyramide	Levofloxacin	Sulpiride
Dofetilide	Levomepromazine	Sultopride
Domperidone	Levosulpiride	Terlipressin
Donepezil	Methadone	Thioridazine

Data Source: crediblemeds.org revision date 09 January 2017.

The above table is not exhaustive and prohibited drugs are defined by the online version at the time of screening of the subject

Section 6.11.2.3 – Cautionary Medications

Rationale for Change:

Based on FDA review and emerging safety data from the BET115521 monotherapy study, it was suggested that the study limit the use of certain medications. Revision of Table 8 to provide updated list of Prohibited Medication from May 2016 and addition of footnote to Table.

Previous text:

If a subject requires medication for hyperemesis, due to the potential of serotonin 5-HT3 receptor antagonists to increase QTcF, palonosetron (up to a maximum dose of 0.25 mg daily) and ondansetron (up to a maximum oral dose of 8 mg TID) are the only allowed drugs in this class (dolasetron and granisetron are not permitted). Drugs with a low risk of causing QTc prolongation (e.g., aprepitant) may be used without restriction.

Co-administration of GSK525762 and the following medications requires extreme caution beginning 14 days prior to the first dose of study drug until discontinuation from the study, due to an increased risk of Torsades de Pointes. These medications include (but are not limited to):

Drugs with a Risk of Torsades de Pointes which are permitted for co-administration with Extreme Caution

Alfuzosin	Iloperidone	Ranolazine
Apomorphine	Imipramine	Rilpivirine
Aripiprazole	Isradipine	Risperidone
Artenimole+piperaquine		Roxithromycin
Asenapine	Mifepristone	Saquinavir
Atazanavir	Lithium	Sertindole
Atomoxetine	Mifepristone	Tacrolimus
Bedaquiline	Mirabegron	Telavancin
Clomipramine	Mirtazapine	Telithromycin
Clozapine	Moexipril/ hydrochlorothiazide	Tetrabenazine
Delamanid	Nortriptyline	Tizanidine
Desipramine	Ofloxacin	Tolterodine
Dexmedetomidine	Olanzapine	Toremifene
Famotidine	Oxytocin	Trimipramine
Felbamate	Paliperidone	Tropisetron
Fingolimod	Pasireotide	Vardenafil
Foscarnet	Perflutren lipid microspheres	Venlafaxine
Gemifloxacin	Pipamperone	
Hydrocodone ER	Promethazine	

Data Source: crediblemeds.org revision date 17 Dec 2015

Revised text:

Subjects should minimize the use of medications which contain acetaminophen. Subjects should be informed of alternative medications.

If a subject requires medication for hyperemesis, due to the potential of serotonin 5-HT3 receptor antagonists to increase QTcF, palonosetron (**administered per the prescribing information**~~up to a maximum dose of 0.25 mg daily~~) and oral ondansetron (up to a maximum oral dose of 8 mg TID) are the only allowed drugs in this class (dolasetron and granisetron are not permitted). Drugs with a low risk of causing QTc prolongation (e.g., aprepitant) may be used without restriction.

Co-administration of GSK525762 and the following medications requires extreme caution beginning 14 days prior to the first dose of study drug until discontinuation from the study, due to an increased risk of Torsades de Pointes. These medications include (but are not limited to):

Drugs with a Risk of Torsades de Pointes which are permitted for co-administration with Extreme Caution

Alfuzosin	Foscarnet	Perphenazine
Apomorphine	Gemifloxacin	Pipamperone
Aripiprazole	Hydrocodone ER	Promethazine
Artenimole+piperaquine	Iloperidone	Rilpivirine
Asenapine	Imipramine	Risperidone
Atomoxetine	Isradipine	Saquinavir
Bedaquiline	Leuprolide	Sertindole
Buprenorphine	Lithium	Solifenacin
Clomipramine	Melperone	Tacrolimus
Clozapine	Mifepristone	Telavancin
Cyamemazine	Mirabegron	Telithromycin
Degarelix	Mirtazapine	Tetrabenazine
Delamanid	Moexipril/ hydrochlorothiazide	Tiapride
Desipramine	Nicardipine	Tizanidine
Dexmedetomidine	Norfloxacin	Tolterodine
Efavirenz	Nortriptyline	Trimipramine
Ezogabine	Ofloxacin	Tropisetron
Famotidine	Oxytocin	Vardenafil
Felbamate	Paliperidone	Venlafaxine
Fingolimod	Pasireotide	Zotepine
Flupentixol	Perflutren lipid microspheres	

Data Source: crediblemeds.org revision date 09 January 2017

The above table is not exhaustive and prohibited drugs are defined by the online version at the time of screening of the subject

Section 7.1 – Time and Events Tables

Rationale for Change:

Revision to the Dose Escalation and Dose Expansion table of events and associated laboratory tables. For study assessment tables, these were modified to include a column for possible lead-in abiraterone or enzalutamide dosing, clarification for weeks for every 4 weeks and every 8 weeks and addition of column for revised every 12 weeks scheduling post Week 49. Adjustment to footnotes 11, 13, 16, and 17. For the laboratory tables, these were adjusted to add in a clarification of visits for every 4 weeks, addition of column for revised every 12 weeks scheduling post Week 49, additional row to clarify testing of Factor VII assay. Addition of footnotes 1 and 2.

Previous text:

Table 9 Dose Escalation Time and Events

Procedure	SCR	Week 1		Week 2		Week 3		Week 4	Week 5	q4w	q8w	EOT[1, 22]
		D 1	D 4	D 1	D 4	D 1	D 4	D 1	D 1	W9 and thereafter	W9 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
ECOG	X	X		X		X		X	X	X		X
12-lead ECGs (Triplicate)[6]	X	X	X	X		X		X	X	X		X
Clinical Laboratory Assessments[7]	X	X	X	X	X	X	X	X	X	X		X
Echocardiogram or MUGA[8]	X										X	X
PRO-CTCAE[9]	X	X		X		X		X	X	X		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										

Procedure	SCR	Week 1		Week 2		Week 3		Week 4	Week 5	q4w	q8w	EOT [1, 22]
		D1	D4	D1	D4	D1	D4	D1	D1	W9 and thereafter	W9 and thereafter	
Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)												
PK blood samples[12]		PK				PK			O		X	
Tumor biopsy[13]	X						One sample, collected 3-6h post-GSK525762 dose, between W3D1 and W4D1					X[14]
Whole blood for exploratory analyses	X	X					X[15]			Week 9 only	Week 13, q8w after	X
PGx blood sample		X										
Biomarker Assessments												
CTC-ENU[16]	X	X							X		X	X
CTC – ARV[17]	X	X							X	Week 9 only		X
Efficacy												
Computerized Tomography (CT) chest/abdomen/pelvis[18]	X										Q8wks up to six months, then Q12wks	X
MRI Brain[19]	X											
Bone Scan[20]	X										Q8wks up to six months, then Q12wks	
EORTC-QLQ-C30, EORTC-QLQ-PR25 & BPI-SF[21]	X	X		X		X		X	X	X		X

11. 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.
13. Paired fresh biopsies must be provided pre- and post-dose at time points indicated. If it is not feasible to obtain a fresh biopsy, an archival sample must be provided. Fresh biopsies should be paired with plasma and whole blood samples for PK and circulating biomarkers collected as close as possible to biopsy (ideally within 1h). Refer to the SRM for further details.

16. CTC-ENU: Whole blood samples will be obtained for CTC enumeration at Screening; pre-dose on W1D1, W5D1 of the combination treatment period; thereafter, pre-dose every 8 weeks during treatment; and EOT.
17. CTC-ARV: Whole blood samples will be obtained for measuring AR-Vs at pre-dose on Screening, W1D1, W5D1, and W9D1 of the combination treatment period; and EOT.

Table 10 Dose Escalation Time and Events, Laboratory Assessments

		Week 1		Week 2		Week 3		Week 4	Week 5	q4w	
	SCR	D1	D4	D1	D4	D1	D4	D1	D1	W9 and thereafter	EOT
Clinical chemistry	X	X	X	X		X		X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X[1]	X
Liver chemistry	X	X	X	X	X	X	X	X	X	X	X
Troponin, N-terminal pro–B-Type natriuretic peptide (NT-proBNP)	X	X	X	X	X	X	X	X	X	X	X
Coagulation	X	X	X	X		X		X	X	X	X
HbA1c	X								X	X	X
Fasting lipids	X								X	X	X
Thyroid stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4))	X								X	X	X
Pancreatic Markers	X	X		X		X		X	X	X	X
Urinalysis	X	X		X		X		X	X	X	X
HIV, Hepatitis B surface antigen (HBsAg), Hepatitis C Virus (HCV) Antibody	X										
PSA	X	X							X	X	X
Testosterone	X										X

Table 11 Dose Expansion Time and Events

		Week 1	Week 2	Week 3	Week 4	Week 5	q4w	q8w	EOT[1, 22]
Procedure	SCR	D1	D1	D1	D1	D1	W9 and thereafter	W9 and thereafter	
Screening[2]									
Informed Consent	X								
Demography	X								

Procedure	SCR	Week 1 D1	Week 2 D1	Week 3 D1	Week 4 D1	Week 5 D1	q4w W9 and thereafter	q8w W9 and thereafter	EOT[1, 22]
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
ECOG	X	X	X	X	X	X	X		X
12-lead ECGs (Triplicate)[6]	X	X	X	X	X	X	X		X
Clinical Laboratory Assessments[7]	X	X	X	X	X	X	X		X
Echocardiogram or MUGA[8]	X							X	X
PRO-CTCAE[9]	X	X	X	X	X	X	X		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							
Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)									
PK blood samples[12]		PK		PK		O		X	
Tumor biopsy[13]	X			One sample, collected 3-6h post-GSK525762 dose, between W3D1 and W4D1					X[14]
Whole blood for exploratory analyses	X	X		X[15]			Week 9 only	Week 13, q8w after	X
PGx blood sample		X							
Biomarker Assessments									
CTC-ENU[16]	X	X				X		X	X
CTC – ARV[17]	X	X				X	Week 9 only		X
Efficacy									
Computerized Tomography (CT) chest/abdomen/pelvis[18]	X							Q8wks up to six months, then Q12wks	X
MRI Brain[19]	X								

Procedure	SCR	Week 1 D1	Week 2 D1	Week 3 D1	Week 4 D1	Week 5 D1	q4w W9 and thereafter	q8w W9 and thereafter	EOT[1, 22]
Bone Scan[20]	X							Q8wks up to six months, then Q12wks	
EORTC-QLQ-C30, EORTC-QLQ-PR25 & BPI-SF[21]	X	X	X	X	X	X	X		X

11. 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.
13. Paired fresh biopsies must be provided pre- and post-dose at time points indicated. If it is not feasible to obtain a fresh biopsy, an archival sample must be provided. Fresh biopsies should be paired with plasma and whole blood samples for PK and circulating biomarkers collected as close as possible to biopsy (ideally within 1h). . Refer to the SRM for further details.
16. CTC-ENU: Whole blood samples will be obtained for CTC enumeration at Screening; pre-dose on W1D1, W5D1 of the combination treatment period; thereafter, pre-dose every 8 weeks during treatment; and EOT.
17. CTC-ARV: Whole blood samples will be obtained for measuring AR-Vs at pre-dose on Screening, W1D1, W5D1, and W9D1 of the combination treatment period; and EOT.

Table 12 Dose Expansion Time and Events, Laboratory Assessments

	SCR	Week 1 D1	Week 2 D1	Week 3 D1	Week 4 D1	Week 5 D1	q4w W9 and thereafter	EOT
Clinical chemistry	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X[1]	X
Liver chemistry	X	X	X	X	X	X	X	X
Troponin, N-terminal pro–B-Type natriuretic peptide (NT- proBNP)	X	X	X	X	X	X	X	X
Coagulation	X	X	X	X	X	X	X	X
HbA1c	X					X	X	X
Fasting lipids	X					X	X	X
Thyroid (Thyroid stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4))	X					X	X	X
Pancreatic Markers	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X
HIV, Hepatitis B surface antigen (HBsAg), Hepatitis C Virus (HCV) Antibody	X							
PSA	X	X				X	X	X
Testosterone	X							X

Revised text:

Table 9 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]
			D 1	D 4	D 1	D 4	D 1	D 4	D 1	D 1	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 (Triplicate)[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**							**X**	**Weeks 13, 25 and 37**	~~X~~	**X**	X
PRO-CTCAE[9]	X		X		X		X		X	X	X		**X**	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											

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**	
Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)														
PK blood samples[12]			PK				PK			O		X		
Tumor biopsy[13]	X							One sample, collected 3-6h post-GSK525762 dose, between W3D1 and W4D1						X[14]
Whole blood for exploratory analyses	X		X					X[15]				**Q8wks up to six months, then Q12 wks**	**X**	X
PGx blood sample			X											
Biomarker Assessments														
CTC-ENU[16]	X		X							X		**Q8wks up to six months, then Q12wks**	**X**	X
CTC – ARV[17]			X							X	Week 9 only			X
Efficacy														
Computerized Tomography (CT) chest/abdomen/pelvis[18]	X											Q8wks up to six months, then Q12 wks	**X**	X
MRI Brain[19]	X													

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**	
Bone Scan[20]	X											Q8wks up to six months, then Q12 wks	**X**	
EORTC-QLQ-C30, EORTC-QLQ-PR25 & BPI-SF[21]	X		X		X		X		X	X	X		**X**	X

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.
13. Paired fresh biopsies must be provided pre- and post-dose at time points indicated. If it is not feasible to obtain a fresh biopsy, an archival sample must be provided. Fresh biopsies should be paired with plasma and whole blood samples for PK and circulating biomarkers collected as close as possible to biopsy (ideally within 1h). **Subjects must have a platelet count of ≥75,000/mm3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy.** Refer to the SRM for further details.
16. CTC-ENU: Whole blood samples will be obtained for CTC enumeration at Screening; pre-dose on **W1D1 of the combination treatment period,** W5D1**, W9D1 and every 8 weeks for the first 6 months and thereafter every 12 weeks;** ~~of the combination treatment period; thereafter, pre-dose every 8 weeks during treatment;~~ and EOT.
17. CTC-ARV: Whole blood samples will be obtained for measuring AR-Vs at pre-dose on ~~Screening,~~ W1D1, W5D1, and W9D1 of the combination treatment period; and EOT. **Based on emerging data, GSK may decide to discontinue the collection of these samples.**

Table 10 Dose Escalation Time and Events, Laboratory Assessments

		Week 1		Week 2		Week 3		Week 4	Week 5	q2w	q4w	**q4W**	**q12w**	
	SCR	D1	D4	D1	D4	D1	D4	D1	D1	W7 and 11	W9 **to W49**	**W49 and thereafter**	**W49 and thereafter**	EOT
Clinical chemistry	X	X	X	X		X		X	X	**X[2]**	X	**X[2]**	**X**	X
Hematology	X	X	X	X	X	X	X	X	X	**X[2]**	X[1]	**X[2]**	**X**	X
Liver chemistry	X	X	X	X	X	X	X	X	X	**X[2]**	X	**X[2]**	**X**	X
Troponin, N-terminal pro–B-Type natriuretic peptide (NT-proBNP)	X	X	X	X	X	X	X	X	X		X		**X**	X
Coagulation	X	X	X	X		X		X	X	**X[2]**	X	**X[2]**	**X**	X
Factor VII Assay[1]	**X**					**X**			**X**					
HbA1c	X								X		X		**X**	X
Fasting lipids	X								X		X		**X**	X
Thyroid stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4))	X								X		X		**X**	X
Pancreatic Markers	X	X		X		X		X	X		X		**X**	X
Urinalysis	X	X		X		X		X	X		X		**X**	X
HIV, Hepatitis B surface antigen (HBsAg), Hepatitis C Virus (HCV) Antibody	X													
PSA	X	X							X		X	**X[2]**	**X**	X
Testosterone	X													X

1. **In addition to scheduled timepoints, perform if PT or INR or aPTT are ≥1.5XULN, or in case of a bleeding event.**
2. **Local labs can be used to collect this information.**

Table 11 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	D 1	D 1	D 1	D 1	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 (Triplicate)[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**				**X**	**Weeks 13, 25 and 37**	~~X~~	**X**	X
PRO-CTCAE[9]	X		X	X	X	X	X	X		**X**	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]			PK		PK		O		X		
Tumor biopsy[13]	X				One sample, collected 3-6h post-GSK525762 dose, between W3D1 and W4D1						X[14]

Procedure	SCR	**Lead-In Dosing (if required)**	Week 1 D1	Week 2 D 1	Week 3 D 1	Week 4 D 1	Week 5 D 1	q4w W9 **to W49**	q8w W9 **to W49**	**q12w** **W49 and thereafter**	EOT [1, 22]
Whole blood for exploratory analyses	X		X		X[15]				**Q8wks up to six months, then Q12wks**	**X**	X
PGx blood sample			X								
Biomarker Assessments											
CTC-ENU[16]	X		X				X		**Q8wks up to six months, then Q12wks**	**X**	X
CTC – ARV[17]			X				X	Week 9 only			X
Efficacy											
CT chest/abdomen/pelvis[18]	X								Q8wks up to six months, then Q12wks	**X**	X
MRI Brain[19]	X										
Bone Scan[20]	X								Q8wks up to six months, then Q12wks	**X**	
EORTC-QLQ-C30, **EORTC-QLQ-PR25** & BPI[21]	X		X	X	X	X	X	X		**X**	X

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.

13. Paired fresh biopsies must be provided pre- and post-dose at time points indicated. If it is not feasible to obtain a fresh biopsy, an archival sample must be provided. Fresh biopsies should be paired with plasma and whole blood samples for PK and circulating biomarkers collected as close as possible to biopsy (ideally within 1h). **Subjects must have a platelet count of ≥75,000/mm3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy.** Refer to the SRM for further details.
16. CTC-ENU: Whole blood samples will be obtained for CTC enumeration at Screening; pre-dose on **W1D1 of the combination treatment period,** W5D1**, W9D1 and every 8 weeks for the first 6 months and thereafter every 12 weeks;** ~~of the combination treatment period; thereafter, pre-dose every 8 weeks during treatment;~~ and EOT.
17. CTC-ARV: Whole blood samples will be obtained for measuring AR-Vs at pre-dose on ~~Screening,~~ W1D1, W5D1, and W9D1 of the combination treatment period; and EOT. **Based on emerging data, GSK may decide to discontinue the collection of these samples.**

Table 12 Dose Expansion Time and Events, Laboratory Assessments

	SCR	Week 1	Week 2	Week 3	Week 4	Week 5	q2w	q4w	**q4W**	**q12w**	EOT
		D1	D1	D1	D1	D1	W7 and 11	W9 **to W49**	**W49 and thereafter**	**W49 and thereafter**	
Clinical chemistry	X	X	X	X	X	X	**X[2]**	X	**X[2]**	**X**	X
Hematology	X	X	X	X	X	X	**X[2]**	X[1]	**X[2]**	**X**	X
Liver chemistry	X	X	X	X	X	X	**X[2]**	X	**X[2]**	**X**	X
Troponin, N-terminal pro–B-Type natriuretic peptide (NT-proBNP)	X	X	X	X	X	X		X		**X**	X
Coagulation	X	X	X	X	X	X	**X[2]**	X	**X[2]**	**X**	X
Factor VII Assay[1]	**X**			**X**		**X**					
HbA1c	X					X		X		**X**	X
Fasting lipids	X					X		X		**X**	X
Thyroid stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4))	X					X		X		**X**	X
Pancreatic Markers	X	X	X	X	X	X		X		**X**	X
Urinalysis	X	X	X	X	X	X		X		**X**	X
HIV, Hepatitis B surface antigen (HBsAg), Hepatitis C Virus (HCV) Antibody	X										
PSA	X	X				X		X	**X[2]**	**X**	X
Testosterone	X										X

1. **In addition to scheduled timepoints, perform if PT or INR or aPTT are ≥1.5XULN, or in case of a bleeding event.**
2. **Local labs can be used to collect this information.**

Section 7.2.2 – Visit Windows

Rationale for Change:

Clarification to this section to reflect change of timing when visits shift to less frequent visit; clarified the timeframe and additional assessments and updated wording to section.

Previous text:

Every 4-week and 8-week visits after Week 9 until Week 52: After the first disease assessment has been completed, then the clinic visits can be scheduled ± 5 days.

Every 4-week and 8-week visits after Week 52: Every 4 week visits (and their associated laboratory studies) are no longer required, based on clinical judgment. Every 8-week clinic visits can be scheduled ± 7 days. Disease assessments will only be required every 16 weeks and can be scheduled ± 7 days.

Revised text:

Every 4-week and 8-week visits after Week 9 until Week **49**~~52~~**:** After the first disease assessment has been completed, then the clinic visits can be scheduled ± 5 days.

Every **12**4 week ~~and 8 week~~ visits after **Week 49**~~52~~**: 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 4 week visits (and their associated laboratory studies) are no longer required, based on clinical judgment.~~ Every ~~8~~**12**-week clinic visits can be scheduled ± 7 days. ~~Disease assessments will only be required every 16 weeks and can be scheduled ± 7 days.~~

Section 7.3.5 – Clinical Safety Laboratory Assessments

Rationale for Change:

Clarification that Factor VII assay should be completed under the Other Stuides section of the Laboratory Assessments, highlighted in Table 13.

Previous text:

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:**
	Hemoglobin A1c	Amylase
	PSA	Lipase
	Testosterone	

Revised text:

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:**
	Hemoglobin A1c	Amylase
Factor VII Assay	PSA	Lipase
	Testosterone	

Section 7.3.7 – Pregnancy

Rationale for Change:

Based on safety team review, added Pregnancy information that is needed in this male only study.

New text:

Details of all pregnancies in female partners of male subjects will be collected after the start of dosing and until at least 4 months post-last dose.

If a pregnancy is reported then the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 12.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

Section 7.4 – Pharmacokinetics

Rationale for Change:

Removal of wording to prevent confusion on what PK samples are being analysed. All abiraterone PK samples will be analysed.

Previous text:

Blood samples for pharmacokinetic (PK) analysis of abiraterone/enzalutamide and GSK525762 (including relevant metabolite(s)) will be collected at the time points

indicated in Table 9, Table 10, Table 11, and Table 12. While GSK525762 PK samples will be collected at all time points starting on Week 1 Day 1, only the pre dose samples will be analysed for abiraterone/enzalutamide. The actual date and time of each blood sample collection will be recorded. Subjects should be instructed to withhold their dose of orally administered study drugs, including GSK525762 and abiraterone/enzalutamide, until after the pre-dose pharmacokinetic blood sample is collected.

Revised text:

Blood samples for pharmacokinetic (PK) analysis of abiraterone/enzalutamide and GSK525762 (including relevant metabolite(s)) will be collected at the time points indicated in Table 9, Table 10, Table 11, and Table 12. ~~While GSK525762 PK samples will be collected at all time points starting on Week 1 Day 1, only the pre dose samples will be analysed for abiraterone/enzalutamide.~~ The actual date and time of each blood sample collection will be recorded. Subjects should be instructed to withhold their dose of orally administered study drugs, including GSK525762 and abiraterone/enzalutamide, until after the pre-dose pharmacokinetic blood sample is collected.

Section 7.5.1 – Tumor Biopsy Collection

Rationale for Change:

Updated title to include Surgical Procedures. Added additional requirements based on emerging safety data.

Previous text:

In the dose escalation and expansion cohort(s), paired fresh biopsies must be provided pre- (within 14 days of the first dose) and on-treatment at the time points indicated from all the subjects. Any fresh on-treatment biopsy should be accompanied by a whole blood sample collected as close as possible to the time of biopsy (preferably within 1h). Further details regarding sample type and processing will be provided in the SRM. If a potential subject does not have disease amenable to biopsy, participation may occur only upon discussion with and approval of the medical monitor; in this situation, an archival tumor sample retrieved after completion of most recent ADT will be required.

Further details regarding sample type and processing will be provided in the SRM.

Revised text:

In the dose escalation and expansion cohort(s), paired fresh biopsies must be provided pre- (within 14 days of the first dose) and on-treatment at the time points indicated from all the subjects. Any fresh on-treatment biopsy should be accompanied by a whole blood sample collected as close as possible to the time of biopsy (preferably within 1h). **Subjects providing an on-treatment fresh tumor biopsy must have received at least 4 consecutive days of GSK525762 prior to the collection of the sample.** Further details regarding sample type and processing will be provided in the SRM. If a potential subject does not have disease amenable to biopsy, participation may occur only upon discussion

with and approval of the medical monitor; in this situation, an archival tumor sample retrieved after completion of most recent ADT will be required.

Subjects must have a platelet count of ≥75,000/mm3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy or any other planned surgical procedure. Further details regarding sample type and processing will be provided in the SRM.

Section 7.7.3 – Circulating Tumor Cells

Rationale for Change:

Added language that would allow flexibility on collection of CTC-ARV samples.

Previous text:

Additional blood samples will be collected at the time points indicated in the Time and Events Tables (Section 7.1) to isolate CTCs. The isolated CTCs will be analyzed for AR variants or other protein markers and potential genomic alterations (e.g. AR amplifications, phosphatase and tensin homolog (PTEN) allele loss etc.).

Revised text:

Additional blood samples will be collected at the time points indicated in the Time and Events Tables (Section 7.1) to isolate CTCs. The isolated CTCs will be analyzed for AR variants or other protein markers and potential genomic alterations (e.g. AR amplifications, phosphatase and tensin homolog (PTEN) allele loss etc.). **Based on emerging data, GSK may decide to discontinue the collection of these samples.**

Section 9.3.1 – Analysis Populations

Rationale for Change:

Added another population group to clarify how to handle data from subjects who may withdraw during the run-in period.

Previous text:

The **All Treated Population** is defined as all subjects who receive at least one dose of GSK525762 plus abiraterone/enzalutamide. Safety and anti-cancer activity will be evaluated based on this analysis population.

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

Revised text:

The All Treated Safety Population is defined as all subjects who receive at least one dose of GSK525762 or abiraterone or enzalutamide. Safety and anti-cancer activity will be evaluated based on this analysis population.

The All **Clinical Activity** Treated Population is defined as all subjects who receive at least one dose of GSK525762 plus abiraterone/enzalutamide. Safety and anti-cancer activity will be evaluated based on this analysis population.

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

Section 9.4.1 – Safety Analyses

Rationale for Change:

Clarification of population to use for analyses due to update to population section.

Previous text:

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

Revised text:

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

Appendix 2 – Management of Suspected Toxicity

Rationale for Change:

Revisions to the Thrombocytopenia section of the Dose Adjustment/Stopping Safety Criteria table based on agreement with the FDA.

Previous text:

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Thrombocytopenia	Grade 1 & 2)	Continue dosing at same dose level with weekly or more frequent monitoring as necessary.
	Grade 3 (platelets <50,000, ≥25,000/mm^3)	Withhold GSK525762 and check activated partial thromboplastin time (aPTT), PT, and INR. Monitor CBC and coagulation studies at least twice a week, or more frequently if clinically indicated. Hold GSK525762 until thrombocytopenia has resolved to ≤Grade 2 AND aPTT, PT, and INR are all ≤ ULN. Drug may then be restarted at lower dose level, after discussion with medical monitor. If safety lab abnormalities recur following rechallenge, drug may be discontinued or restarted at a lower dose level, after discussion with medical monitor.
	Grade 4 (platelets <25,000/mm^3),or any moderate to severe bleeding accompanied by drug related thrombocytopenia	Withhold GSK525762 and check aPTT, PT, and INR. Monitor CBC and coagulation studies every 2-3 days. Hold GSK525762 until thrombocytopenia has resolved to ≤Grade 2 AND aPTT, PT, and INR are all ≤ ULN. Drug may then be restarted at a lower dose level, after discussion with medical monitor. If safety lab abnormalities recur following rechallenge, drug may be discontinued until platelet count recovers to Grade 2 (≥50,000/mm^3). For subjects with moderate to severe bleeding requiring transfusion support, GSK525762 should be permanently discontinued. If platelet count does not recover to ≥50,000/mm^3 (Grade 2) within 14 days, GSK525762 should be permanently discontinued. If platelet count recovers to ≥50,000/mm^3 (Grade 2) within 14 days, GSK525762 may be continued at the current/reduced dose after discussion with the medical monitor.

Revised text:

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Thrombocytopenia	Grade 1 **(platelets <LLN to ≥75,000/mm^3)** & **Grade** 2 **(platelets <75,000 to ≥50,000/mm^3)**	Continue dosing at same dose level with weekly or more frequent monitoring as necessary.
	Grade 3 (platelets <50,000, ≥25,000/mm^3)	Withhold GSK525762 and check activated partial thromboplastin time (aPTT), PT, and INR. Monitor CBC and coagulation studies at least twice a week, or more frequently if clinically indicated. Hold GSK525762 until thrombocytopenia has resolved to ≤Grade 2 AND aPTT, PT, and INR are all ≤ ULN. Drug may then be restarted ~~at the same dose or~~ at a ~~lower~~ dose level **lower**, after discussion with medical monitor. If safety lab abnormalities recur following rechallenge, drug may be discontinued or restarted at **another dose level** lower~~dose level~~, after discussion with medical monitor. **If safety lab abnormalities recur to the same level following a second rechallange, drug will be discontinued.**
	Grade 4 (platelets <25,000/mm^3),or any moderate to severe bleeding accompanied by drug related thrombocytopenia	Withhold GSK525762 and check aPTT, PT, and INR. Monitor CBC and coagulation studies every 2-3 days. Hold GSK525762 until thrombocytopenia has resolved to ≤Grade 2 AND aPTT, PT, and INR are all ≤ ULN. Drug may then be restarted at a lower dose level, after discussion with medical monitor. If safety lab abnormalities recur following rechallenge, drug may be discontinued until platelet count recovers to Grade 2 (≥50,000/mm^3). For subjects with moderate to severe bleeding requiring transfusion support, GSK525762 should be permanently discontinued. If platelet count does not recover to ≥50,000/mm^3 (Grade 2) within 14 days, GSK525762 should be permanently discontinued. If platelet count recovers to ≥50,000/mm^3 (Grade 2) within 14 days, GSK525762 may be continued at the current/reduced dose after discussion with the medical monitor. **If platelet count does not recover to ≥25,000/mm^3 (Grade 3) within 7 days, GSK525762 should be permanently discontinued.**

Appendix 12 - Contraception and Pregnancy Information

Rationale for change:

Section was not included in original protocol as this is a male only study and contraception language was in Section 6.10.2. After additional safety review, decision was made to add Appendix per protocol template and to give further information for male subjects and female partners of reproductive potential. References added also in this section but not captured in this section.

New text:

Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

The list does not apply to male subjects with partners of FRP who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Contraceptive requirements for male subjects with female partners of reproductive potential (when applicable)

Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until 4 month after the last dose of study medication.

1. **Sterilization with documentation of azoospermia. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview.**
2. **Male condom plus partner use of intrauterine device or intrauterine system.**

Note: Hormonal methods of contraception for female partners of FRP are not permitted since the efficacy of these methods in combination with GSK525762 has not been assessed. Hormone-releasing IUDs are a permitted form of contraception. LHRH-acting agents alone are not considered an adequate form of contraception.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

Collection of Pregnancy Information

- **Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in**

this study. This applies only to subjects who are randomized to receive study medication.

- **After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 weeks of learning of the partner's pregnancy**
- **Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.**
- **Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.**

Other changes to provide additional clarifications or to correct inadvertent errors in previous versions of the protocol:

Title Page:

Updated author list to include new authors: PPD , and PPD and remove PPD .

Table of Contents:

Revision to Table of Contents to reflect changes protocol addressed earlier in this Appendix.

Protocol Synopsis:

Throughout the synopsis, revised by removing references and links as per internal requirements.

List of Abbreviations:

Addition of new abbreviations to table: ORR – Objective Response Rate, PSA50 – Prostate-specific antigen decrease from baseline ≥50%, rPFS – Radiological progression free survival, and RR – Response rate

Protocol changes for Amendment 2 (08-Feb-2018) from Amendment 1 (01 – Feb-2017)

Protocol Amendment 2 applies only to France due to requests from their country agency, Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) and the central Ethics Committee, Comité de Protection des Personnes (CPP) Sud-Est III.

Original text is displayed as strikethrough indicates replaced or removed text. New text is displayed as underline. If applicable, revisions within the tables will be displayed as text or if same revision affects multiple tables, the changes will be summarized; revisions to figures will be displayed first by the old figure, and then followed by the new figure.

List of Specific Changes

Section 1 – Type and Number of Subjects

Rationale for Change:

Per committee request, addition of statement regarding potential number of subjects to be enrolled in France.

Previous text:

Approximately 130 subjects worldwide may be enrolled in the study as a whole.

Revised text:

Approximately 130 subjects worldwide may be enrolled in the study as a whole. In France, approximately 28 subjects are to be enrolled.

Section 1 - Protocol Synopsis Inclusion Criteria

Rationale for Change:

Added wording at the request of the France agency ANSM to clarify patient population.

Previous text:

6. One to two line(s) of prior taxane-based chemotherapy allowed. If docetaxel chemotherapy is used more than once, this will be considered as one regimen.

Revised text:

6. One to two line(s) of prior taxane-based chemotherapy allowed. If docetaxel chemotherapy is used more than once, this will be considered as one regimen. Subjects who have not received prior chemotherapy in any setting will qualify for study if they are ineligible for or refuse chemotherapy.

Section 4.1.1.: Type and Number of Subjects

Rationale for Change:

Per committee request, addition of statement regarding potential number of subjects to be enrolled in France.

Previous text:

Approximately 130 subjects worldwide may be enrolled in the study as a whole.

Revised text:

Approximately 130 subjects worldwide may be enrolled in the study as a whole. In France, approximately 28 subjects are to be enrolled.

Section 4.2.2.1: Planned Dose Levels

Rationale for Change:

Added wording at the request of the France agency ANSM to clarify allowed top dose of GSK525762.

Previous text:

GSK525762 as a single agent is being investigated at the highest dose of 80 mg (amorphous tablet)/ 75 mg (besylate tablet) once daily (Recommended Part 2 Dose, RP2D) in the expansion cohorts of the first time in human solid tumor study (BET115521). All doses of GSK525762 refer to the besylate tablet formulation. For Arm A, projected dose levels of GSK525762 are 60 mg and 80 mg administered once daily. For Arm B, projected dose levels of GSK525762 are 80 mg, and 100 mg administered once daily. A dose of 120 mg may be evaluated in combination with enzalutamide based on emerging PK and safety data. Projected dose levels of abiraterone and enzalutamide are 1000 mg and 160 mg respectively, administered once daily. Additional doses and schedules may be explored based on emerging safety, PK, and PD data. No doses will be explored beyond 1000 mg abiraterone or 160 mg enzalutamide, these doses that are considered to be the Maximum Feasible Dose (MFD), unless emerging PK data demonstrate reduced exposure of either drug in combination compared to single agent. As determined from pre-clinical studies, the maximum clinical dose of GSK525762 will not exceed 200 mg.

Revised text:

GSK525762 as a single agent is being investigated at the highest dose of 80 mg (amorphous tablet)/ 75 mg (besylate tablet) once daily (Recommended Part 2 Dose, RP2D) in the expansion cohorts of the first time in human solid tumor study (BET115521). All doses of GSK525762 refer to the besylate tablet formulation. For Arm A, projected dose levels of GSK525762 are 60 mg and 80 mg administered once daily. For Arm B, projected dose levels of GSK525762 are 80 mg, and 100 mg administered

once daily. A dose of 120 mg may be evaluated in combination with enzalutamide based on emerging PK and safety data. Projected dose levels of abiraterone and enzalutamide are 1000 mg and 160 mg respectively, administered once daily. Additional doses and schedules may be explored based on emerging safety, PK, and PD data. No doses will be explored beyond 1000 mg abiraterone or 160 mg enzalutamide, these doses that are considered to be the Maximum Feasible Dose (MFD), unless emerging PK data demonstrate reduced exposure of either drug in combination compared to single agent. As determined from pre-clinical studies, the maximum clinical dose of GSK525762 will not exceed 200 mg. Any GSK525762 dose above 120 mg would require regulatory authority review and approval.

Section 5.1: Inclusion Criteria

Rationale for Change:

Added wording at the request of the France agency ANSM to clarify patient population.

Previous text:

6. One to two line(s) of prior taxane-based chemotherapy allowed. If docetaxel chemotherapy is used more than once, this will be considered as one regimen.

Revised text:

6. One to two line(s) of prior taxane-based chemotherapy allowed. If docetaxel chemotherapy is used more than once, this will be considered as one regimen. Subjects who have not received prior chemotherapy in any setting will qualify for study if they are ineligible for or refuse chemotherapy.

Section 5.4.1.1: Study Treatment Restart or Rechallenge

Rationale for Change:

Added wording at the request of the France central Ethics Committee, Comité de Protection des Personnes (CPP) Sud-Est III, to clarify restriction for restart and rechallenge in French subjects.

Previous text:

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

- GSK Medical Governance approval **is granted**
- Ethics and/or Institutional Review Board (IRB) approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

Refer to Appendix 7 for full guidance.

Revised text:

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

- GSK Medical Governance approval **is granted**
- Ethics and/or Institutional Review Board (IRB) approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

Refer to Appendix 7 for full guidance.

In France, if stopping criteria is met, subjects will not be allowed to restart or be rechallenged.

Section 5.4.2: QTc Stopping Criteria

Rationale for Change:

Added wording at the request of the France central Ethics Committee, Comité de Protection des Personnes (CPP) Sud-Est III, to clarify restriction for restart and rechallenge in French subjects.

Previous text:

For the purposes of this study, the corrected QT (QTc) is the QT interval corrected for heart rate according to Fridericia's formula (QTcF; defined as $[QT/(RR^{1/3})]$). QTcF will be used for all subjects for purposes of eligibility, data analysis, and withdrawal. The QTcF should be based on averaged QTcF values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

Study treatments will be withheld if either of the following occurs:

- QTcF interval ≥500 msec
- QTcF interval increase from baseline ≥60 msec

In either case, both GSK525762 and abiraterone/enzalutamide will be discontinued unless the benefits of therapy outweigh the risk of rechallenge in the opinion of the investigator, the Medical Monitor, as well as GSK medical governance. In this situation, rechallenge may be permitted (see Appendix 2 for rechallenge guidelines).

Revised text:

For the purposes of this study, the corrected QT (QTc) is the QT interval corrected for heart rate according to Fridericia's formula (QTcF; defined as $[QT/(RR^{1/3})]$). QTcF will be used for all subjects for purposes of eligibility, data analysis, and withdrawal. The QTcF should be based on averaged QTcF values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

Study treatments will be withheld if either of the following occurs:

- QTcF interval ≥500 msec
- QTcF interval increase from baseline ≥60 msec

In either case, both GSK525762 and abiraterone/enzalutamide will be discontinued unless the benefits of therapy outweigh the risk of rechallenge in the opinion of the investigator, the Medical Monitor, as well as GSK medical governance. In this situation, rechallenge may be permitted (see Appendix 2 for rechallenge guidelines).

In France, if stopping criteria is met, subjects will not be allowed to restart or be rechallenged.

Appendix 2 – Management of Suspected Toxicity

Rationale for Change:

Revisions to the QTcF and Liver Chemistry stopping criteria section of the Dose Adjustment/Stopping Safety Criteria table based on agreement with the French agency, ANSM and the France central Ethics Committee, Comité de Protection des Personnes (CPP) Sud-Est III, to clarify restriction for restart and rechallenge in French subjects.

Previous text:

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
QTcF	If >30msec and < 60 msec change from baseline AND manual QTcF <500 (average of three ECGs over at least 15 minutes)	Continue current dose of GSK525762 • Supplement electrolytes, particularly potassium and magnesium, to recommended levels: a. Maintain serum potassium > 4mol/L b. Maintain serum magnesium levels >0.85 mmol/L • Discontinue any concomitant medications with potential for QTcF prolongation. • Consider 24 hour or longer telemetry monitoring if clinically indicated.

	If ≥ 60 msec change from baseline occurs OR QTcF ≥500 (average of three ECGs over at least 15 minutes)	Discontinue GSK525762 and notify the Medical Monitor. • Supplement electrolytes to recommended levels: a. Maintain serum potassium > 4mol/L b. Maintain serum magnesium levels >0.85 mmol/L • Rule out other potential etiologies for prolonged QTcF such as cardiac ischemia • Discontinue any concomitant medications with potential for QTcF prolongation. • Consider telemetry monitoring if clinically indicated. This subject may consider restarting study treatment at one dose level reduced if all of the following criteria for QTcF re-challenge are met. If approval for re-challenge is granted, the subject must be re-consented (with a separate informed consent specific to QTc prolongation) (1) QTcF reduced to <450 msec, (2) Potassium and magnesium levels are within institutional normal range, (3) A favorable risk/benefit profile (in the medical judgement of the Investigator and the Medical Monitor), (4) Approval within GSK medical governance: a. agreement with SERM MD and PPL, b. review with Chair or co-Chair of the GSK QT panel, c. SERM VP and Clinical VP approval d. Head Unit Physician approval (5) Institutional IRB (or equivalent) approval, and (6) The subject is re-consented regarding the possible increased risk of QTc prolongation. Discontinuation procedures: If the subject is withdrawn due to QTcF event, the subject should complete the following activities post-dose: (1) Evaluation by cardiologist. (2) Weekly assessments for QTcF should be performed for two weeks, and then next assessment at 4 weeks post-dose. (3) If QTcF results have not resolved to baseline by 4 weeks post-dose, then continue every 4-5 weeks until resolution

Liver	• ALT ≥5X ULN, OR • ALT ≥3X ULN plus either bilirubin ≥2X ULN (>35% direct bilirubin, bilirubin fractionation required) or INR >1.5 without evidence of biliary obstruction or progressive disease, OR ALT ≥3X ULN plus symptoms of liver injury or hypersensitivity[a]	Refer to Section 5.4.1 for liver chemistry stopping criteria and treatment algorithms, and to Appendix 7 for reporting and follow-up of suspected liver events. For subjects who develop hepatotoxicity during treatment, hold abiraterone until recovery. Retreatment may be initiated at a reduced dose of 750 mg QD following return of liver function tests to baseline. If hepatotoxicity recurs at dose of 750 mg QD, reduce dose to 500 mg QD following return of liver function tests to baseline. If hepatotoxicity recurs at 500 mg, discontinue treatment with abiraterone.

Revised text:

Toxicity	**Dose Adjustment/ Stopping Criteria**	**Management Guidelines**
QTcF	If >30msec and < 60 msec change from baseline AND manual QTcF <500 (average of three ECGs over at least 15 minutes)	Continue current dose of GSK525762 • Evaluation by cardiologist • Supplement electrolytes, particularly potassium and magnesium, to recommended levels: a. Maintain serum potassium > 4mol/L b. Maintain serum magnesium levels >0.85 mmol/L • Discontinue any concomitant medications with potential for QTcF prolongation. • Consider 24 hour or longer telemetry monitoring if clinically indicated.

	If ≥ 60 msec change from baseline occurs OR QTcF ≥500 (average of three ECGs over at least 15 minutes)	Discontinue GSK525762 and notify the Medical Monitor. • Evaluation by cardiologist • Supplement electrolytes to recommended levels: a. Maintain serum potassium > 4mol/L b. Maintain serum magnesium levels >0.85 mmol/L • Rule out other potential etiologies for prolonged QTcF such as cardiac ischemia • Discontinue any concomitant medications with potential for QTcF prolongation. • ~~Consider~~ **24-hour** telemetry monitoring if clinically indicated. This subject may consider restarting study treatment at one dose level reduced if all of the following criteria for QTcF re-challenge are met. In France, if stopping criteria is met, subjects will not be allowed to restart or be rechallenged. If approval for re-challenge is granted, the subject must be re-consented (with a separate informed consent specific to QTc prolongation) (1) QTcF reduced to <450 msec, (2) Potassium and magnesium levels are within institutional normal range, (3) A favorable risk/benefit profile (in the medical judgement of the Investigator and the Medical Monitor), (4) Approval within GSK medical governance: a. agreement with SERM MD and PPL, b. review with Chair or co-Chair of the GSK QT panel, c. SERM VP and Clinical VP approval d. Head Unit Physician approval (5) Institutional IRB (or equivalent) approval, ~~and~~ if required by IRB (or equivalent), and (6) The subject is re-consented regarding the possible increased risk of QTc prolongation. Discontinuation procedures: If the subject is withdrawn due to QTcF event, the subject should complete the following activities post-dose: (1) Evaluation by cardiologist. (2) Weekly assessments for QTcF until ≤30 msec change from baseline reached ~~should be performed for two weeks~~, and then next assessment at 4 weeks post-dose. (3) If QTcF results have not resolved to baseline by 4 weeks post-dose, then continue every 4-5 weeks until resolution

Liver	• ALT ≥5X ULN, OR • ALT ≥3X ULN plus either bilirubin ≥2X ULN (>35% direct bilirubin, bilirubin fractionation required) or INR >1.5 without evidence of biliary obstruction or progressive disease, OR ALT ≥3X ULN plus symptoms of liver injury or hypersensitivity[a]	Refer to Section 5.4.1 for liver chemistry stopping criteria and treatment algorithms, and to Appendix 7 for reporting and follow-up of suspected liver events. <u>In France, if stopping criteria is met, subjects will not be allowed to restart or be rechallenged.</u> For subjects who develop hepatotoxicity during treatment, hold abiraterone until recovery. Retreatment may be initiated at a reduced dose of 750 mg QD following return of liver function tests to baseline. If hepatotoxicity recurs at dose of 750 mg QD, reduce dose to 500 mg QD following return of liver function tests to baseline. If hepatotoxicity recurs at 500 mg, discontinue treatment with abiraterone.

Appendix 7 – Management of Suspected Toxicity

Rationale for Change:

Added wording at the request of the France central Ethics Committee, Comité de Protection des Personnes (CPP) Sud-Est III, to clarify restriction for restart and rechallenge in French subjects.

Previous text:

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

- GSK Medical Governance approval **is granted** (as described below),
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

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

Revised text:

<u>In France, if stopping criteria is met, subjects will not be allowed to restart or be rechallenged.</u>

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

- GSK Medical Governance approval **is granted** (as described below),
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

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

Protocol changes for Amendment 3 (12-Jul-2018) from Amendment 1 (01-Feb-2017) and France specific Amendment (08-Feb-2018)

Protocol Amendment 3 applies to all global site(s) participating in the conduct of the study

Amendment 3 Summary

Amendment 3 includes the following changes which incorporate revisions based on internal and external feedback and a change in the abiraterone formulation: updates to sponsor information; further clarification of L2 line of therapy; addition of new secondary endpoint; clarification of PSA progression definition for endpoint analysis; update to dose utility wording and other statistical analysis updates; enhanced flexibility of dose level/schedule; modifications to inclusion/exclusion criteria; updated safety language based on current Investigator's Brochure; revision to QTc wording due to GSK safety panel recommendations and associated prohibited medication language; inclusion of 500 mg abiraterone to replace 250 mg abiraterone; clarification to dose reduction language; revisions to Time and Events including removal of Week 1 ECHO/MUGA, AR-V sampling post screening, adjustment to screening and tumor biopsy windows; addition of Week 6 lab sample per safety panel recommendation; modifications to Appendix 2 to reflect QTc changes; and Appendix 8 to remove protocol specific SAE wording. Additions are underlined and deletions have been struck through.

Original text is displayed as strikethrough indicates replaced or removed text. New text is displayed as underline. If applicable, revisions within the tables will be displayed as text or if same revision affects multiple tables, the changes will be summarized; revisions to figures will be displayed first by the old figure, and then followed by the new figure. Administrative changes, such as minor wording changes that do not affect the intent of a statement, will not be displayed in the summary of changes.

List of Specific Changes

Section 1 - Protocol Synopsis Rationale

Rationale for Change:

Revision of language regarding BET115521 which has closed.

Previous text:

Recent studies have shown an alternate mode of AR inhibition by targeting a new class of proteins known as bromodomain and extraterminal domains (BET). Studies have demonstrated that BET inhibition can lead to growth arrest and cell death in a variety of preclinical models, including models of CRPC. An ongoing first-in-human (FIH) study from GlaxoSmithKline (GSK), BET115521, is currently evaluating the safety and preliminary efficacy of single-agent GSK525762, a potent inhibitor of BET proteins, in a number of tumor types including mCRPC. Preliminary data from the futility analysis of the CRPC arm indicated there were no partial or complete responses. This data will be further examined as the data continues to mature.

Revised text:

Recent studies have shown an alternate mode of AR inhibition by targeting a new class of proteins known as bromodomain and extraterminal domains (BET). Studies have demonstrated that BET inhibition can lead to growth arrest and cell death in a variety of preclinical models, including models of CRPC. The~~An ongoing~~ first-in-human (FIH) study from GlaxoSmithKline (GSK), BET115521, evaluated~~is currently evaluating~~ the safety and preliminary efficacy of single-agent GSK525762, a potent inhibitor of BET proteins, in a number of tumor types including mCRPC. Preliminary data from the futility analysis of the CRPC arm indicated there were no partial or complete responses. This data will be further examined as the data continues to mature.

Section 1 - Protocol Synopsis Rationale

Rationale for Change:

Update of L2 definition to clarify allowance of 1 prior line of chemotherapy.

Previous text:

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]) 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]).

Revised text:

… 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])…

Section 1 - Protocol Synopsis Objective(s)/Endpoint(s)

Rationale for Change:

Addition of new secondary endpoint and clarifications/reorder of other secondary endpoints.

Previous text:

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	• PK parameter or concentration values for abiraterone or enzalutamide following repeat-dose oral administration in combination with

with mCRPC	GSK525762
• To evaluate additional measures of clinical activity in subjects with CRPC • To evaluate the effect of treatment with GSK525762 and abiraterone or enzalutamide, when given in combination, on patient-related outcomes	• Objective Response Rate (ORR) defined as complete response (CR) rate plus partial response (PR) rate per Prostate Cancer 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 at 4 weeks • Time to disease progression according to PCWG3 criteria (either by PCWG3-modified RECIST 1.1, PSA progression, and/or progression in bone) • Radiological progression free survival (rPFS) per PCWG3-modified RECIST1.1 • 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 • Performance status, pain scores, quality of life

Revised text:

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	• <u>For both arms, clinical activity evaluated by disease control rate (DCR) through 24 weeks.</u> • <u>Composite Response Rate (CRR) based on any of the following – a) Response based on PCWG3-modified RECIST1.1, b) PSA decrease</u>

	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 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 ~~at~~ 4 weeks of study treatment. • Time to disease progression according to PCWG3 criteria (either by PCWG3-modified RECIST 1.1, ~~PSA progression, and/~~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 • ~~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~~ • Performance status, pain scores, quality of life
• To evaluate the effect of treatment with GSK525762 and abiraterone or enzalutamide, when given in combination, on patient-related outcomes	

Section 1 - Protocol Synopsis Overall Design

Rationale for Change:

Revision of futility dose utility wording based on input from Berry Consulting and updates necessary to clarify intent of analyses.

Previous text:

… For the separate interim looks in each combination in expansion cohort, the enrollment for that cohort may be stopped due to futility if the predictive probability that the expected utility (dU) ≥CSMU (30) is small (e.g., less than a 20% chance for the expected utility to be larger than the CSMU).

Revised text:

… 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~~predictive~~ probability that the~~expected~~ utility (dU) ≥CSMU (25~~30~~) is small (e.g., less than a 4~~20~~% chance for the~~expected~~ utility to be larger than the CSMU). Decisions made to stop enrolment in any cohort will be based on the totality of the data, including safety/tolerability and efficacy.

Section 1 - Protocol Synopsis Overall Design

Rationale for Change:

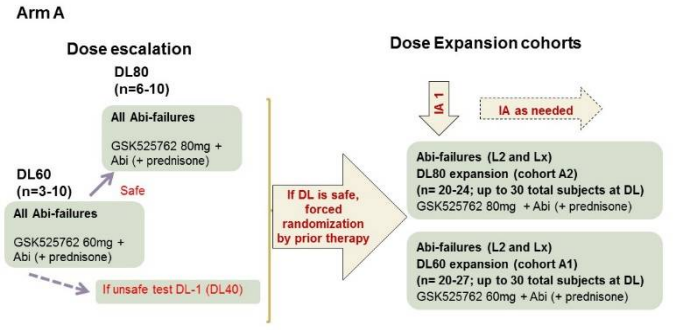
Revisions to Arm A to clarify previous language and add flexible language.

Previous text:

… During dose escalation, eligible subjects in dose level 60 (DL60) will begin dosing with GSK525762 at 60 mg (one dose level lower than the single-agent RP2D), and the approved dose of abiraterone. If DL60 does not exceed the MTD, DL80 (GSK525762 given 80 mg QD) will be opened (Figure 1). Subjects in DL80 will begin dosing with GSK525762 at 80 mg (equivalent to single-agent RP2D), and the approved dose of abiraterone. If DL60 exceeds the maximum permitted toxicity rate, then a lower dose level (DL-1, 40 mg) will be evaluated. If DL80 cohort is opened, but exceeds the maximum permitted toxicity rate, then additional subjects will not be enrolled at DL80.

If DL80 does not exceed MTD, the dose expansion cohorts at both DL60 and DL80 will be initiated and will be randomized by prior lines of therapy (L2 or Lx). A total of 30 subjects each will be enrolled into both cohorts, and approximately10 enrolled subjects will be L2 and 20 subjects will be Lx (Figure 1).

Figure 1



•During dose escalation, a minimum of 3 subjects will be enrolled at DL60. A minimum of 6 subjects are required to DL80 prior to dose expansion.
•IA: interim analysis to stop the arm with very low predictive probability of success on efficacy. To occur after first 10 evaluable subjects per DL. Additional IAs can occur every 10 evaluable subjects. Cohorts may be stopped at any time for futility.
•Each DL may enroll up to 30 subjects. Each DL total (up to 30) will be comprise subjects from treated during dose escalation and dose expansion.
•All Abi-failures: Includes patients that are Abiraterone refractory or resistant from second line and above (L2 or Lx)
•For Abiraterone failed subjects that are off therapy, there will be at least a 7 day lead in with abiraterone before the start of combination

Revised text:

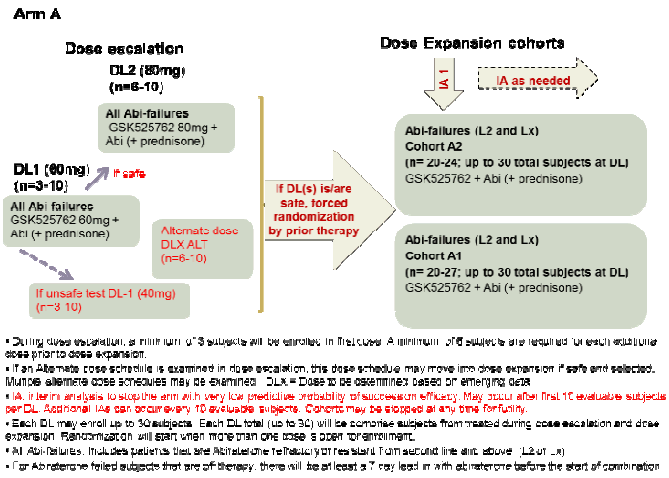
… During dose escalation, eligible subjects will be dosed in at least two dose levels to identify the two dose level cohorts to explore in dose expansion. The approved dose of abiraterone (1000 mg) will be used for all GSK525762 dose level exploration. The initial~~in~~ GSK525762 dose level will be ~~60 (~~dose level 60 mg (DL60), which is one dose level lower than the single-agent RP2D. ~~will begin dosing with GSK525762 at 60 mg (one dose level lower than the single-agent RP2D), and the approved dose of abiraterone.~~

If DL60 does not exceed the MTD, DL80 (GSK525762 given 80 mg QD) will be opened (Figure 1). ~~Subjects in DL80 will begin dosing with GSK525762 at 80 mg (equivalent to single-agent RP2D), and the approved dose of abiraterone. If DL60 exceeds the maximum permitted toxicity rate, then a lower dose level (DL-1, 40 mg) will be evaluated.~~ If any dose level cohort~~DL80 cohort~~ is opened, but exceeds the maximum permitted toxicity rate, then additional subjects will not be enrolled at that dose level. ~~DL80.~~

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 schedule, 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 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 ~~If DL80 does not exceed MTD, the dose expansion cohorts at both DL60 and DL80~~may ~~will~~ be initiated and ~~will be~~ randomized by prior lines of therapy (L2 or Lx). A total of 30 subjects each may ~~will~~ be enrolled into both cohorts, and approximately10 enrolled subjects will be L2 and 20 subjects will be Lx (Figure 1). If only one dose level is tolerable for dose expansion, subjects will be enrolled and not randomized.

Figure 1



Section 1 - Protocol Synopsis Overall Design

Rationale for Change:

Revisions to Arm B to clarify previous language and add flexible language.

Previous text:

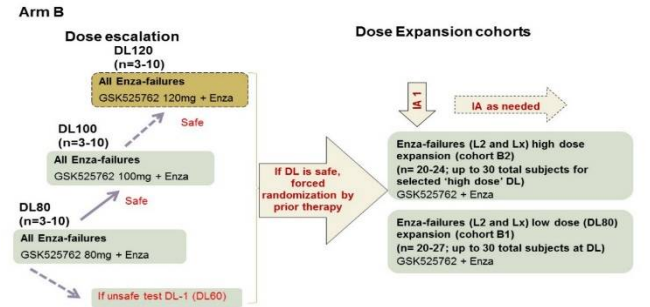
… Eligible subjects will be administered escalating doses of GSK525762 in combination with the approved doses of enzalutamide. As enzalutamide is a known CYP3A4 inducer, DDI could potentially lower the exposure of GSK525762 active moiety levels by 20%. Therefore, subjects will be enrolled at DL80 as the starting dose.

During dose escalation, eligible subjects in dose level 80 (DL80) will begin dosing with GSK525762 at 80 mg (equivalent of single-agent RP2D), and the approved dose of enzalutamide. If DL80 does not exceed the MTD, DL100 (GSK525762 given 100 mg once daily will be opened (Figure 2). Subjects in DL100 will begin dosing with GSK525762 at 100 mg and the approved dose of enzalutamide. If DL80 exceeds the maximum permitted toxicity rate, then a lower dose level (DL-1, 60 mg) will be evaluated. If DL100 cohort is opened, but exceeds the maximum permitted toxicity rate, then additional subjects will not be enrolled at DL100.

However, based on PK analysis from DL80 and DL100 dose escalation cohorts, if the exposure to GSK525762 active moiety is 40% lower than its single agent exposure (determined from GSK525762 80 mg cohort in BET115521 study), DL120 may be opened. The study team will carefully review PK and safety data from the DL80 and DL100 levels to determine if it is acceptable to open the DL120 dose level. If DL120 is opened, subjects in DL120 will begin dosing with GSK525762 at 120 mg and the approved dose of enzalutamide.

Once a higher dose (either DL100 or DL120) and lower dose (DL80) are determined to not exceed the MTD, the dose expansion cohorts at the selected higher and lower doses will be initiated and will be randomized by prior lines of therapy (L2 or Lx). A total of 30 subjects each will be enrolled into both cohorts, and approximately10 enrolled subjects will be L2 and 20 subjects will be Lx (Figure 2).

Figure 2



•During dose escalation, a minimum of 3 subjects will be enrolled per each opened Dose Level. Determination of the 'high dose' (either DL100 or DL120) will need to include a minimum of 6 subjects to confirm safe 'high' dose prior to dose expansion.
•IA: interim analysis to stop the arm with very low predictive probability of success on efficacy. To occur after first 10 evaluable subjects per DL. Additional IAs can occur every 10 evaluable subjects. Cohorts may be stopped at any time for futility.
•Each DL may enroll up to 30 subjects. Each DL total (up to 30) will be comprise subjects from treated during dose escalation and dose expansion.
•All Enza-failures: Includes patients that are Enzalutamide refractory or resistant from second line and above (L2 or Lx)
•For Enzalutamide failed subjects that are off therapy, there will be at least 14-28 day lead in with enzalutamide before the start of combination

Revised text:

… Eligible subjects will be administered escalating doses of GSK525762 in combination with the approved dose~~s~~ of enzalutamide (160 mg). As enzalutamide is a known CYP3A4 inducer, DDI could potentially lower the exposure of GSK525762 active moiety levels by 20%. Therefore, subjects will be enrolled at DL80 as the starting dose.

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 initial ~~in~~ GSK525762 dose level will be ~~80 (~~dose level 80 mg (DL80), which is equivalent to one dose level lower than the single-agent RP2D due to expected DDI. ~~will begin dosing with GSK525762 at 80 mg (equivalent of single-agent RP2D), and the approved dose of~~

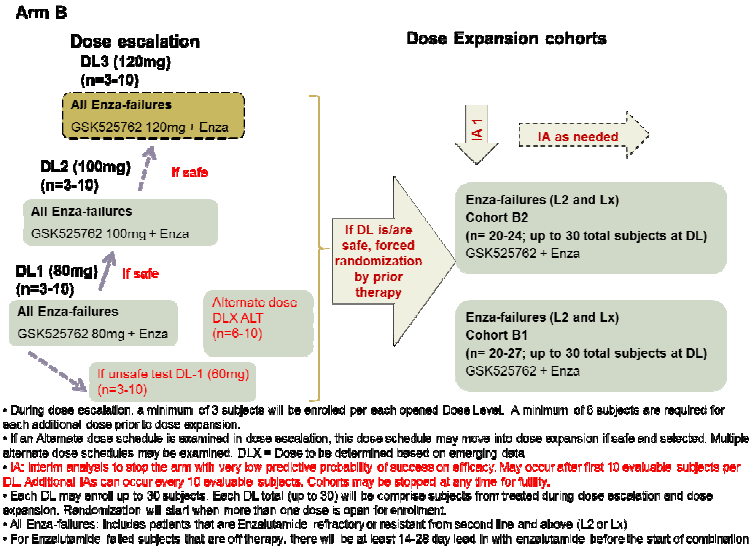
~~enzalutamide.~~ If DL80 does not exceed the MTD, DL100 (GSK525762 given 100 mg QD) ~~once daily~~ will be opened (Figure 2). ~~Subjects in DL100 will begin dosing with GSK525762 at 100 mg and the approved dose of enzalutamide. If DL80 exceeds the maximum permitted toxicity rate, then a lower dose level (DL-1, 60 mg) will be evaluated.~~ If any dose level cohort~~DL100 cohort~~ is opened, but exceeds the maximum permitted toxicity rate, then additional subjects will not be enrolled at that dose level. ~~DL100.~~

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 schedule, either at a dose level where daily treatment may be intolerable or at a lower dose. For example, if DL80 exceeds the maximum permitted toxicity rate, then intermittent dosing at 80 mg dose level (DL80 ALT) and/or a lower daily dose level (DL-1, 60 mg) may be evaluated.

~~However, b~~Based on PK analysis from DL80 and DL100 dose escalation cohorts, if the exposure to GSK525762 active moiety is 40% lower than its single agent exposure (determined from GSK525762 80 mg cohort in BET115521 study), DL120 may be opened. The study team will carefully review PK and safety data from the DL80 and DL100 levels to determine if it is acceptable to open the DL120 dose level. If DL120 is opened, subjects in DL120 will begin dosing with GSK525762 at 120 mg and the approved dose of enzalutamide.

To further explore and identify the MTDs (and RP2Ds), the two most tolerable dose levels ~~Once a higher dose (either DL100 or DL120) and a lower dose (DL80) are determined to not exceed MTD, the dose expansion cohorts at the selected higher and lower doses~~ may ~~will~~ be initiated and ~~will be~~ randomized by prior lines of therapy (L2 or Lx). A total of 30 subjects each may ~~will~~ be enrolled into both cohorts, and approximately10 enrolled subjects will be L2 and 20 subjects will be Lx (Figure 2). If only one dose level is tolerable for dose expansion, subjects will be enrolled and not randomized.

Figure 2



Section 1 - Protocol Synopsis Treatment Arms and Duration

Rationale for Change:

Clarification of term change from BET to product number, adjustment of other language in section.

Previous text:

… For subjects receiving GSK525762 in combination with abiraterone, daily administration of combination therapy (GSK525762 plus abiraterone) will commence immediately (Day 1) for abiraterone-failed subjects who are still on abiraterone (i.e., not stopped abiraterone dosing at progression and during screening). However, if these subjects are off abiraterone treatment for more than 3 days at the time of assignment to a cohort, there would be a lead in period for at least 7 days of abiraterone (Day7 to Day 0) before the start of combination treatment (GSK525762 plus abiraterone on Day 1). The lead-in dosing will ensure that abiraterone is at steady state upon initiation of BET treatment. Based on emerging information collected from PK, PD and safety/tolerability data, other dosing regimens (such as BID dosing for both drugs or intermittent dosing for GSK525762 or staggered dosing of the two drugs) may be explored during the study.

For subjects receiving GSK525762 in combination with enzalutamide, daily administration of combination therapy (GSK525762 plus enzalutamide) will commence immediately (Day 1) for enzalutamide-failed subjects who are still on enzalutamide (i.e. not stopped enzalutamide dosing at progression and during screening). However, if these subjects are off enzalutamide treatment for more than 7 days at the time of assignment to a cohort, there would be a lead in period for at least 28 days of enzalutamide (Day 28 to Day 0) before the start of combination treatment (GSK525762 and enzalutamde). There will be a 14 day lead in period if enzalutamide (Day -14 to Day 0) interruption was less than or equal to 7 days prior to start of combination treatment (Day 1). The lead-in dosing will ensure that enzalutamide is at steady state upon initiation of BET treatment. Based upon emerging data, additional subjects may be enrolled above, at, or below the combination doses mentioned previously, in order to collect additional safety and PK data.

Initial dosing will maintain a fixed dose of abiraterone (1000 mg daily) or enzalutamide (160 mg daily). GSK525762 as a single agent is being investigated at the highest dose of 80 mg (amorphous tablet)/ 75 mg (besylate tablet) once daily (Recommended Phase 2 Dose, RP2D) in the expansion cohorts of the first time in human solid tumor study (BET115521). Doses beyond the single-agent RP2D may be explored if the drug is tolerated and PK analysis demonstrates reduced GSK525762 exposure (Area under concentration-time curve [AUC] and/or maximum observed concentration [Cmax]) when administered in combination with enzalutamide. Dose reductions for individual subjects may be required, based on toxicity observed during the study, and the frequency and duration of dose reductions will be reported. If enzalutamide is discontinued for more than or equal to 7 days, then the maximum dose of GSK525762 should be the single agent RP2D of 80 mg. If enzalutamide is re-started, GSK525762 should remain at 80 mg until after at least 14 days until the dose is escalated, if applicable. Subjects who require permanent discontinuation of either abiraterone or enzalutamide in the combination may continue GSK525762 as a single agent if there is evidence of continuing benefit on

treatment. If GSK525762 is continued as a single agent, the maximum dose would be 80 mg. Intra-subject dose escalations from the planned starting dose during dose escalation will not be permitted. Intra-subject dose escalation may be permitted during dose expansion if for the lower dose level only if that dose is determined to be futile.

Revised text:

… For subjects receiving GSK525762 in combination with abiraterone, daily administration of combination therapy (GSK525762 plus abiraterone) will commence immediately (Day 1) for abiraterone-failed subjects who are still on abiraterone (i.e., not stopped abiraterone dosing at progression and during screening). However, if these subjects are off abiraterone treatment for more than 3 days at the time of assignment to a cohort, there would be a lead in period for at least 7 days of abiraterone (Day -7 to Day 0) before the start of combination treatment (GSK525762 plus abiraterone on Day 1). The lead-in dosing will ensure that abiraterone is at steady state upon initiation of ~~BET~~ GSK525762 treatment. ~~Based on emerging information collected from PK, PD and safety/tolerability data, other dosing regimens (such as BID dosing for both drugs or intermittent dosing for GSK525762 or staggered dosing of the two drugs) may be explored during the study.~~

For subjects receiving GSK525762 in combination with enzalutamide, daily administration of combination therapy (GSK525762 plus enzalutamide) will commence immediately (Day 1) for enzalutamide-failed subjects who are still on enzalutamide (i.e. not stopped enzalutamide dosing at progression and during screening). However, if these subjects are off enzalutamide treatment for more than 7 days at the time of assignment to a cohort, there would be a lead in period for at least 28 days of enzalutamide (Day -28 to Day 0) before the start of combination treatment (GSK525762 and ~~enzalutamde~~enzalutamide). There will be a 14 day lead in period if enzalutamide (Day -14 to Day 0) interruption was less than or equal to 7 days prior to start of combination treatment (Day 1). The lead-in dosing will ensure that enzalutamide is at steady state upon initiation of GSK525762~~BET~~ treatment. Based upon emerging data, additional subjects may be enrolled above, at, or below the combination doses mentioned previously, in order to collect additional safety and PK data.

Initial dosing will maintain a fixed dose of abiraterone (1000 mg daily) or enzalutamide (160 mg daily). GSK525762 as a single agent was ~~is being~~ investigated at the highest dose of 80 mg (amorphous tablet)/ 75 mg (besylate tablet) once daily (Recommended Phase 2 Dose, RP2D) in the expansion cohorts of the first time in human solid tumor study (BET115521). Doses beyond the single-agent RP2D may be explored if the drug is tolerated and PK analysis demonstrates reduced GSK525762 exposure (Area under concentration-time curve [AUC] and/or maximum observed concentration [Cmax]) when administered in combination with enzalutamide. Dose reductions for individual subjects may be required, based on toxicity observed during the study, and the frequency and duration of dose reductions will be reported. If enzalutamide is discontinued for more than or equal to 7 days, then the maximum dose of GSK525762 should be the single agent RP2D of 80 mg. If enzalutamide is re-started, GSK525762 should remain at 80 mg until after at least 14 days until the dose is escalated, if applicable. Subjects who require permanent discontinuation of either abiraterone or enzalutamide in the combination may continue GSK525762 as a single agent if there is evidence of continuing benefit on

treatment. If GSK525762 is continued as a single agent, the maximum dose would be 80 mg. Intra-subject dose escalations from the planned starting dose during dose escalation will not be permitted. Intra-subject dose escalation may be permitted during dose expansion if for the lower dose level only if that dose is determined to be futile.

Based on emerging information collected from PK, PD and safety/tolerability data, other dosing regimens (such as intermittent dosing for GSK525762 or staggered dosing of the two drugs) may be explored during the study.

Section 1 - Protocol Synopsis Inclusion Criteria

Rationale for Change:

Revisions to wording of specific criteria to correct or clarify original wording and revise based on investigator feedback/internal decisions. Only the criteria which has been affected will be listed in both Previous and Revised sections.

Previous text:

3. Histologically confirmed adenocarcinoma of the prostate:

   b. Screening biopsy can be waived if patient had a recent biopsy after failure of ADT therapy (within 30 days) and the biopsy sample is secured to be sent as screening biopsy for this study.

4. Surgically or medically castrated, with testosterone levels of ≤ 50 ng/dL (<2.0 nM). If the patient is being treated with LHRH agonists/antagonists (patient who have not undergone orchiectomy) this therapy must have been initiated at least 4 weeks prior to Cycle 1 Day 1 and must be continued throughout the study.

5. Subjects must have failed prior therapy with abiraterone, enzalutamide, or both

   a. Has completed at least 12 weeks of prior continuous therapy with abiraterone or enzalutamide

   b. Has not been without abiraterone or enzalutamide treatment for >30 days prior to initiation of study treatment

6. One to two line(s) of prior taxane-based chemotherapy allowed. If docetaxel chemotherapy is used more than once, this will be considered as one regimen.

7. Documented prostate cancer progression as assessed by the investigator with one of the following:

   a. PSA progression defined by a minimum of 3 rising PSA levels with an interval of ≥1 week between each determination. The PSA value at screening must be ≥5 ug/L (5 ng/mL) if PSA is the only indication of progression; subjects on systemic glucocorticoids for control of symptoms must have documented PSA progression by PCWG3 while on systemic glucocorticoids prior to commencing Cycle 1 Day 1 treatment.

   b. Radiographic progression of soft tissue disease by PCWG3-modified RECIST 1.1 criteria or bone metastasis with 2 or more documented new bone lesions on a bone scan with or without PSA progression

11. Adequate organ function as defined in Table 1:

System	Laboratory Values
Cardiac	
Ejection fraction	≥ lower limit of normal (LLN) by echocardiogram or multigated acquisition scan (MUGA) and minimum of 50% LVEF

12. Male subject with a female partner of childbearing potential or pregnant must agree to use two acceptable methods of contraception from time of first dose of study treatment until 4 months after the last dose of study treatments.

Revised text:

3. Histologically confirmed adenocarcinoma of the prostate:

   b. Screening biopsy can be waived if patient had a recent biopsy after failure of ~~ADT therapy~~ the most recent therapy (within 30 days) and the biopsy sample is secured to be sent as screening biopsy for this study.

4. Surgically or medically castrated, with testosterone levels of ≤ 50 ng/dL (<2.0 nM). If the patient is being treated with LHRH agonists/antagonists (patient who have not undergone orchiectomy) this therapy must have been initiated at least 4 weeks prior to Week 1 ~~Cycle 1~~ Day 1 and must be continued throughout the study.

5. Subjects must have failed prior therapy with abiraterone, enzalutamide, or both

   a. Has completed at least 12 weeks of prior continuous therapy with abiraterone or enzalutamide in any prior line

   ~~b. Has not been without abiraterone or enzalutamide treatment for >30 days prior to initiation of study treatment~~

6. One to two line(s) of prior taxane-based chemotherapy allowed. If docetaxel chemotherapy is used more than once, this will be considered as one regimen. Subjects who have not received prior chemotherapy in any setting will qualify for study if they are ineligible for or refuse chemotherapy.

7. Documented prostate cancer progression as assessed by the investigator with one of the following:

   a. PSA progression defined by a minimum of 3 rising PSA levels with an interval of ≥1 week between each determination. The PSA value at screening must be ≥5 ug/L (5 ng/mL) if PSA is the only indication of progression; subjects on systemic glucocorticoids for control of symptoms must have documented PSA progression by PCWG3 while on systemic glucocorticoids prior to commencing Week~~Cycle~~ 1 Day 1 treatment.

   b. Radiographic progression of soft tissue disease by PCWG3-modified RECIST 1.1 criteria or bone metastasis with 2 or more documented new bone lesions on a bone scan/ CT scan with or without PSA progression

11. Adequate organ function as defined in Table 1:

System	Laboratory Values
Cardiac	
Ejection fraction	≥ lower limit of normal (LLN) by echocardiogram or multigated acquisition scan (MUGA) and minimum of 50% LVEF
Troponin (I or T)	≤ ULN

12. ~~Male subject with a female partner of childbearing potential or pregnant must agree to use two acceptable methods of contraception from time of first dose of study treatment until 4 months after the last dose of study treatments~~. Male Participants: Contraceptive use by men or female partner should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

    Male participants are eligible to participate if they agree to the following during the intervention period and for at least 16 weeks after the last dose of study treatment:
    - Refrain from donating sperm

    PLUS either:
    - 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.

Section 1 - Protocol Synopsis Exclusion Criteria

Rationale for Change:

Revisions to wording of specific criteria to correct or clarify original wording and revise based on investigator feedback/internal decisions. Only the criteria which has been affected will be listed in both Previous and Revised sections.

Previous text:

1. Surgery or local prostatic intervention (excluding a prostatic biopsy) less than 28 days of Cycle 1 Day 1.
5. Cardiac abnormalities as evidenced by any of the following:
    a. Baseline QT duration corrected for heart rate by Fridericia's formula (QTcF) interval ≥450 msec
8. Concurrent use of high dose aspirin (doses up to 81 mg oral dose daily allowed) 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
12. History of seizure or any condition that may predispose subject to seizure (e.g., prior cortical stroke or significant brain trauma).

15. Subjects who have experienced a seizure or seizures within 6 months of study treatment or who are currently being treated with cytochrome P450 enzyme inducing anti-epileptic drugs for seizures (use of anti-epileptic drugs to control pain is allowed in subjects not suffering from seizures unless drug is excluded due to CYP3A4 induction - phenytoin, carbamazepine, phenobarbital).

16. Current use of a prohibited medication or planned use of any forbidden medications during treatment with GSK525762 and abiraterone/enzalutamide. This includes medications with significant risk of Torsades de pointes as well as those that are potent inducers or inhibitors of CYP3A4 enzymes or strong inhibitors of CYP2C8.

20. Initiating bisphosphonate or denosumab therapy or adjusting dose/regimen within 3 months prior to Cycle 1 Day 1. Subjects on a stable bisphosphonate or denosumab therapy are eligible and may continue.

Revised text:

1. Surgery or local prostatic intervention (excluding a prostatic biopsy) less than 28 days of Week~~Cycle~~ 1 Day 1.

5. Cardiac abnormalities as evidenced by any of the following:

   a. Baseline QT duration corrected for heart rate by Fridericia's formula (QTcF) interval ≥48~~5~~0 msec

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

12. History of seizure within 6 months of first dose of study treatment or any condition that may predispose subject to seizure (e.g., prior cortical stroke or significant brain trauma) or who are currently being treated with cytochrome P450 enzyme inducing anti-epileptic drugs for seizures (use of anti-epileptic drugs to control pain is allowed in subjects not suffering from seizures unless drug is excluded due to CYP3A4 induction - phenytoin, carbamazepine, phenobarbital).

~~15. Subjects who have experienced a seizure or seizures within 6 months of study treatment or who are currently being treated with cytochrome P450 enzyme inducing anti-epileptic drugs for seizures (use of anti-epileptic drugs to control pain is allowed in subjects not suffering from seizures unless drug is excluded due to CYP3A4 induction - phenytoin, carbamazepine, phenobarbital).~~

15. Current use of a prohibited medication or planned use of any forbidden medications during treatment with GSK525762 and abiraterone/enzalutamide. This includes medications ~~with significant risk of Torsades de pointes as well as those~~ that are potent inducers or inhibitors of CYP3A4 enzymes or strong inhibitors of CYP2C8.

19. Initiating bisphosphonate or denosumab therapy or adjusting dose/regimen within 3 months prior to Week~~Cycle~~ 1 Day 1. Subjects on a stable bisphosphonate or denosumab therapy are eligible and may continue.

Section 1 - Protocol Synopsis Analysis

Rationale for Change:

Revision of wording to clarify intent of analyses, add and modify secondary endpoints, and add minor language changes.

Previous text:

The dose escalation will follow a mTPI design to identify the MTD(s) of GSK525762 in combination with either abiraterone or enzalutamide. A Bayesian adaptive design will be employed which allows the trial to be frequently monitored with the constraint of both Type I and Type II error rates. An initial interim analysis in each cohort will be performed once 10 evaluable subjects have enrolled in that cohort, inclusive of subjects in both dose escalation and dose expansion. Enrolment to an individual cohort may be stopped early for toxicity or meeting futility criteria, but cohorts will not be stopped early if the response rate meets or exceeds the alternate hypothesis at the interim analyses….

… 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.

The following secondary responses will also be considered for drawing conclusions on the clinical activity of the combination(s):

- Time to disease progression according to PCWG3 criteria (either by PCWG3-modified RECIST 1.1, PSA progression, and/or progression in bone)

Revised text:

The dose escalation will follow a mTPI design to identify the MTD(s) of GSK525762 in combination with either abiraterone or enzalutamide. A Bayesian adaptive design will be employed which allows the trial to be frequently monitored with the constraint of both Type I and Type II error rates. An initial interim analysis in each cohort may~~will~~ be performed when at least~~once~~ 10 evaluable subjects have been enrolled in that cohort, inclusive of subjects in both dose escalation and dose expansion. Enrolment to an individual cohort may be stopped early for toxicity or meeting futility criteria, but cohorts will not be stopped early if the response rate meets or exceeds the alternate hypothesis at the interim analyses. Decisions to stop enrolment within a cohort will be based on the totality of the data including safety/tolerability and efficacy….

… 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 decrease 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.

In addition to the primary endpoint, the efficacy of each combination cohort will be evaluated based on the totality of all efficacy endpoints (primary and secondary).

The following secondary efficacy endpoints~~responses~~ will also be considered for drawing conclusions on the clinical activity of the combination(s):

- Disease control rate (DCR) at 24 weeks
- 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, ~~and/or progression in bone)~~)

Section 2.2 – Brief Background

Rationale for Change:

Revisions of wording to clarify closure of FTIH study and clarification of L2 definition.

Previous text:

Recent studies have shown an alternate mode of AR inhibition by targeting a new class of proteins known as BET [Wyce, 2013]. The BET family, comprised of bromodomain 2 (BRD), BRD3, BRD4 and BRDT, recognize acetyl groups on the tails of histones and are critical for recruiting transcriptional machinery necessary for gene expression. BRD4 has been shown to interact with AR, and BET inhibition abrogated BRD4 localization to a subset of AR target loci and reduced AR-mediated gene transcription, causing suppression of AR signaling [Assangani, 2014]. Studies have demonstrated that BET inhibition can lead to growth arrest and cell death in a variety of preclinical models, including models of CRPC [Wyce, 2013]. An ongoing first-in-human (FIH) study from GlaxoSmithKline (GSK), BET115521, is currently evaluating the safety and preliminary efficacy of single-agent GSK525762, a potent inhibitor of BET proteins, in a number of tumor types including mCRPC. Preliminary data from the futility analysis of the CRPC arm indicated there were no partial or complete responses. This data will be further examined as the data continues to mature. Preliminary safety and efficacy data is summarized in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2011N113741_07, 2016]….

….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) 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.

Revised text:

Recent studies have shown an alternate mode of AR inhibition by targeting a new class of proteins known as BET [Wyce, 2013]. The BET family, comprised of bromodomain 2 (BRD), BRD3, BRD4 and BRDT, recognize acetyl groups on the tails of histones and are critical for recruiting transcriptional machinery necessary for gene expression. BRD4 has been shown to interact with AR, and BET inhibition abrogated BRD4 localization to a subset of AR target loci and reduced AR-mediated gene transcription, causing suppression of AR signaling [Assangani, 2014]. Studies have demonstrated that BET inhibition can lead to growth arrest and cell death in a variety of preclinical models, including models of CRPC [Wyce, 2013]. The~~An ongoing~~ first-in-human (FIH) study from GlaxoSmithKline (GSK), BET115521, evaluated~~is currently evaluating~~ the safety and preliminary efficacy of single-agent GSK525762, a potent inhibitor of BET proteins, in a number of tumor types including mCRPC. Preliminary data from the futility analysis of the CRPC arm indicated there were no partial or complete responses. This data will be further examined as the data continues to mature. Preliminary safety and efficacy data is summarized in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2011N113741_07, 201~~6~~8]….

….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.

Section 3. – Objective(s) and Endpoint(s)

Rationale for Change:

Addition of new Secondary Endpoint and revision of wording of other secondary endpoints.

Previous text:

Objectives	Endpoints
Secondary (Both Arms)	
• To evaluate other measures of clinical activity in subjects with CRPC	• ORR defined as CR and PR rate per Prostate Cancer Working Group (PCWG3)-modified Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 • CTC response rate as defined as percent of subjects having favorable (CTC<5/7.5mL) 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 at 4 weeks • Time to disease progression according to PCWG3 criteria (either by PCWG3-modified RECIST 1.1, PSA progression, and/or progression in bone) • rPFS per PCWG3-modified RECIST 1.1 • 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

Revised text:

Objectives	Endpoints
Secondary (Both Arms)	
• To evaluate other measures of clinical activity in subjects with CRPC	• For both arms, clinical activity evaluated by DCR through 24 weeks • 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 • ORR defined as CR and PR rate per Prostate Cancer Working Group (PCWG3)-modified Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 • CTC response rate as defined as percent of subjects having favorable (CTC<5/7.5mL) 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 aftera~~t~~ 4 weeks of study treatment • Time to disease progression according to PCWG3 criteria (either by PCWG3-modified RECIST 1.1 ~~, PSA progression, and/~~or progression in bone or PSA progression with accompanying progression by RECIST 1.1 or bone scan or clinical progression) • rPFS per PCWG3-modified RECIST 1.1 • ~~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~~

Section 4.1. – Overall Design

Rationale for Change:

Revision to language in section to include new secondary endpoint and to modify other secondary endpoint language. Revision of futility dose utility wording based on input from Berry Consulting and updates necessary to clarify intent of analyses.

Previous text:

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) ORR defined as CR and PR rate per PCWG3-modified RECIST 1.1; 2) CTC response rate defined as percent of subjects having favorable CTC <5/7.5mL at nadir if baseline is unfavorable CTC≥5/7.5mL; 3) PSA week 4 response rate defined as percent of subjects achieving ≥30% decrease from baseline PSA at 4 weeks; 4) time to disease progression

according to PCWG3 criteria (either by PCWG3-modified RECIST 1.1, PSA progression, and/or progression in bone); 5) rPFS per PCWG3-modified RECIST 1.1; 6) CRR based on the following – a) response based on PCWG3-modified RECIST 1.1, b) PSA decrease of ≥50%, or c) CTC count conversion. 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 [Lee, 2008] 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 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 predictive probability that the expected utility (dU) ≥CSMU (30) is small (e.g., less than a 20% chance for the expected utility to be larger than the CSMU).

Revised text:

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~~3~~2) CTC response rate defined as percent of subjects having favorable CTC <5/7.5mL at nadir if baseline is unfavorable CTC≥5/7.5mL; 3~~5~~4) PSA week 4 response rate defined as percent of subjects achieving ≥30% decrease from baseline PSA after~~at~~ 4 weeks of study treatment; 6~~5~~4) time to disease progression according to PCWG3 criteria (either by PCWG3-modified RECIST 1.1 or~~, PSA progression, and/or~~ progression in bone or PSA progression with accompanying progression by RECIST 1.1 or bone scan or clinical progression); 7~~6~~5) rPFS per PCWG3-modified RECIST 1.1~~; 76) CRR based on the following – a) response based on PCWG3-modified RECIST 1.1, b) PSA decrease of ≥50%, or c) CTC count conversion~~. 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 ~~[Lee, 2008]~~ 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 ~~expected~~ 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 ~~predictive~~posterior probability that the ~~expected~~ utility (dU) ≥CSMU (25~~30~~) is small (e.g., less than a 4~~20~~% chance for the ~~expected~~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).

Section 4.1 – Overall Design

Rationale for Change:

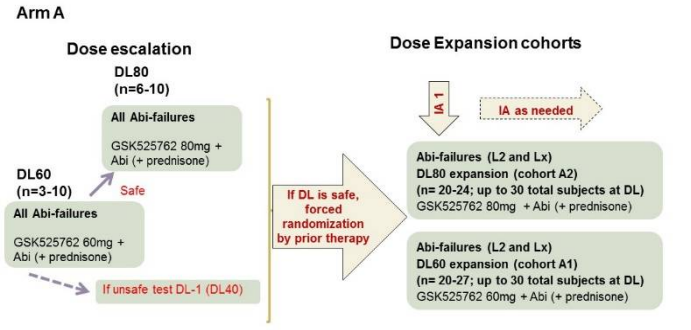
Revisions to Arm A to clarify previous language and add flexible language.

Previous text:

… During dose escalation, eligible subjects in dose level 60 (DL60) will begin dosing with GSK525762 at 60 mg (one dose level lower than the single-agent RP2D), and the approved dose of abiraterone. If DL60 does not exceed the MTD, DL80 (GSK525762 given 80 mg QD) will be opened (Figure 3). Subjects in DL80 will begin dosing with GSK525762 at 80 mg (equivalent to single-agent RP2D), and the approved dose of abiraterone. If DL60 exceeds the maximum permitted toxicity rate, then a lower dose level (DL-1, 40 mg) will be evaluated. If DL80 cohort is opened, but exceeds the maximum permitted toxicity rate, then additional subjects will not be enrolled at DL80.

If DL80 does not exceed MTD, the dose expansion cohorts at both DL60 and DL80 will be initiated and will be randomized by prior lines of therapy (L2 or Lx). A total of 30 subjects each will be enrolled into both cohorts, and approximately10 enrolled subjects will be L2 and 20 subjects will be Lx (Figure 3).

Figure 3



•During dose escalation, a minimum of 3 subjects will be enrolled at DL60. A minimum of 6 subjects are required to DL80 prior to dose expansion.
•IA: interim analysis to stop the arm with very low predictive probability of success on efficacy. To occur after first 10 evaluable subjects per DL. Additional IAs can occur every 10 evaluable subjects. Cohorts may be stopped at any time for futility.
•Each DL may enroll up to 30 subjects. Each DL total (up to 30) will be comprise subjects from treated during dose escalation and dose expansion.
•All Abi-failures: Includes patients that are Abiraterone refractory or resistant from second line and above (L2 or Lx)
•For Abiraterone failed subjects that are off therapy, there will be at least a 7 day lead in with abiraterone before the start of combination

Revised text:

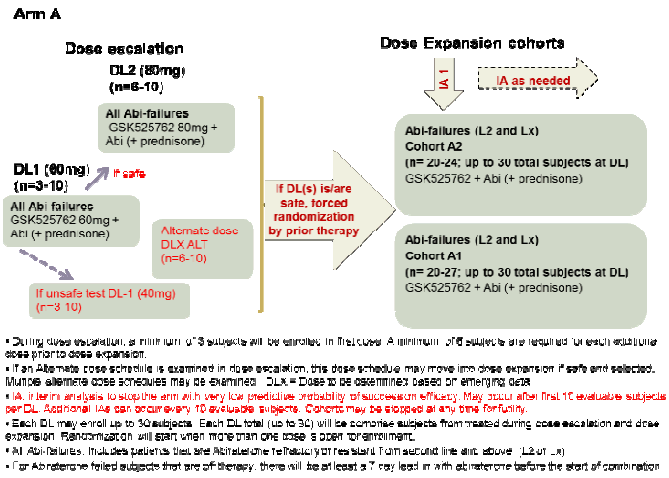
… During dose escalation, eligible subjects will be dosed in at least two dose levels to identify the two dose level cohorts to explore in dose expansion. The approved dose of abiraterone (1000 mg) will be used for all GSK525762 dose level exploration. The initial~~in~~ GSK525762 dose level will be ~~60 (~~dose level 60 mg (DL60), which is one dose level lower than the single-agent RP2D. ~~will begin dosing with GSK525762 at 60 mg (one dose level lower than the single-agent RP2D), and the approved dose of abiraterone.~~

If DL60 does not exceed the MTD, DL80 (GSK525762 given 80 mg QD) will be opened (Figure 3). ~~Subjects in DL80 will begin dosing with GSK525762 at 80 mg (equivalent to single-agent RP2D), and the approved dose of abiraterone. If DL60 exceeds the maximum permitted toxicity rate, then a lower dose level (DL-1, 40 mg) will be evaluated.~~ If any dose level cohort~~DL80 cohort~~ is opened, but exceeds the maximum permitted toxicity rate, then additional subjects will not be enrolled at that dose level. ~~DL80.~~

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 schedule, 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 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 ~~If DL80 does not exceed MTD, the dose expansion cohorts at both DL60 and DL80~~may ~~will~~ be initiated and ~~will be~~ randomized by prior lines of therapy (L2 or Lx). A total of 30 subjects each may ~~will~~ 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.

Figure 3



- During dose escalation, a minimum of 3 subjects will be enrolled in the cohort. A minimum of 6 subjects are required on each evaluable dose prior to dose expansion.
- If an Alternate dose schedule is examined in dose escalation, this dose schedule may move into dose expansion if safe and selected. Multiple alternate dose schedules may be examined. DLX = Dose to be determined based on emerging data
- IA in Lx+ analysis to acquire enough predictive reliability of outcome efficacy. May occur after first 10 evaluable subjects per DL. Additional IAs can occur every 10 evaluable subjects. Cohorts may be stopped at any time for futility.
- Each DL may enroll up to 30 subjects. Each DL total (up to 30) will be combine subjects from treated during dose escalation and dose expansion. Randomization will start when more than one dose is open for enrollment.
- Abi-failures: Includes patients that are Abiraterone refractory or resistant from second line and above (L2 or Lx)
- For Abiraterone naive subjects that are off therapy, there will be at least a 7 day lead in with abiraterone before the start of combination

Section 4.1 - Overall Design

Rationale for Change:

Revisions to Arm B to clarify previous language and add flexible language.

Previous text:

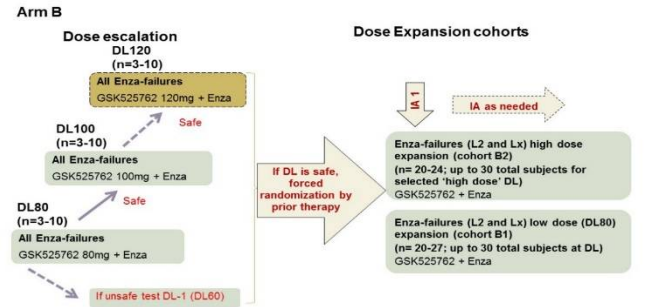
… Eligible subjects will be administered escalating doses of GSK525762 in combination with the approved doses of enzalutamide. As enzalutamide is a known CYP3A4 inducer, DDI could potentially lower the exposure of GSK525762 active moiety levels by 20%. Therefore, subjects will be enrolled at DL80 as the starting dose.

During dose escalation, eligible subjects in dose level 80 (DL80) will begin dosing with GSK525762 at 80 mg (equivalent of single-agent RP2D), and the approved dose of enzalutamide. If DL80 does not exceed the MTD, DL100 (GSK525762 given 100 mg once daily will be opened (Figure 4). Subjects in DL100 will begin dosing with GSK525762 at 100 mg and the approved dose of enzalutamide. If DL80 exceeds the maximum permitted toxicity rate, then a lower dose level (DL-1, 60 mg) will be evaluated. If DL100 cohort is opened, but exceeds the maximum permitted toxicity rate, then additional subjects will not be enrolled at DL100.

However, based on PK analysis from DL80 and DL100 dose escalation cohorts, if the exposure to GSK525762 active moiety is 40% lower than its single agent exposure (determined from GSK525762 80 mg cohort in BET115521 study), DL120 may be opened. The study team will carefully review PK and safety data from the DL80 and DL100 levels to determine if it is acceptable to open the DL120 dose level. If DL120 is opened, subjects in DL120 will begin dosing with GSK525762 at 120 mg and the approved dose of enzalutamide.

Once a higher dose (either DL100 or DL120) and lower dose (DL80) are determined to not exceed the MTD, the dose expansion cohorts at the selected higher and lower doses will be initiated and will be randomized by prior lines of therapy (L2 or Lx). A total of 30 subjects each will be enrolled into both cohorts, and approximately10 enrolled subjects will be L2 and 20 subjects will be Lx (Figure 4).

Figure 4



•During dose escalation, a minimum of 3 subjects will be enrolled per each opened Dose Level. Determination of the 'high dose' (either DL100 or DL120) will need to include a minimum of 6 subjects to confirm safe 'high' dose prior to dose expansion.
•IA: interim analysis to stop the arm with very low predictive probability of success on efficacy. To occur after first 10 evaluable subjects per DL. Additional IAs can occur every 10 evaluable subjects. Cohorts may be stopped at any time for futility.
•Each DL may enroll up to 30 subjects. Each DL total (up to 30) will be comprise subjects from treated during dose escalation and dose expansion.
•All Enza-failures: Includes patients that are Enzalutamide refractory or resistant from second line and above (L2 or Lx)
•For Enzalutamide failed subjects that are off therapy, there will be at least 14-28 day lead in with enzalutamide before the start of combination

Revised text:

… Eligible subjects will be administered escalating doses of GSK525762 in combination with the approved dose~~s~~ of enzalutamide (160 mg). As enzalutamide is a known CYP3A4 inducer, DDI could potentially lower the exposure of GSK525762 active moiety levels by 20%. Therefore, subjects will be enrolled at DL80 as the starting dose.

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 initial ~~in~~ GSK525762 dose level will be ~~80 (~~dose level 80 mg (DL80), which is equivalent to one dose level lower than the single-agent RP2D due to expected DDI. ~~will begin dosing with GSK525762 at 80 mg (equivalent of single-agent RP2D), and the approved dose of~~

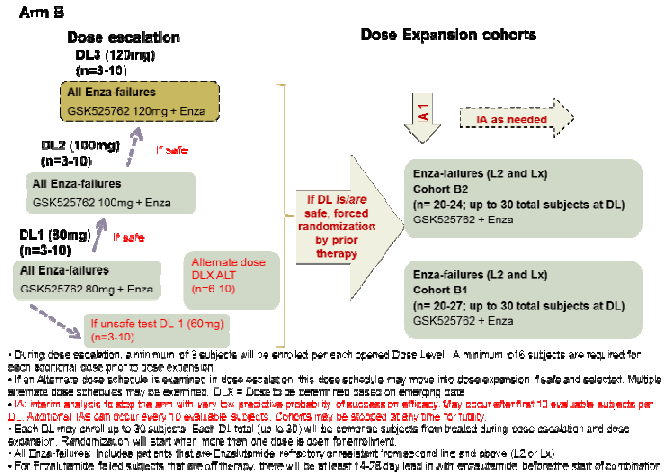
~~enzalutamide.~~ If DL80 does not exceed the MTD, DL100 (GSK525762 given 100 mg QD) ~~once daily~~ will be opened (Figure 2). ~~Subjects in DL100 will begin dosing with GSK525762 at 100 mg and the approved dose of enzalutamide. If DL80 exceeds the maximum permitted toxicity rate, then a lower dose level (DL-1, 60 mg) will be evaluated.~~ If any dose level cohort~~DL100 cohort~~ is opened, but exceeds the maximum permitted toxicity rate, then additional subjects will not be enrolled at that dose level. ~~DL100.~~

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 schedule, either at a dose level where daily treatment may be intolerable or at a lower dose. For example, if DL80 exceeds the maximum permitted toxicity rate, then intermittent dosing at 80 mg dose level (DL80 ALT) and/or a lower daily dose level (DL-1, 60 mg) may be evaluated.

~~However, b~~Based on PK analysis from DL80 and DL100 dose escalation cohorts, if the exposure to GSK525762 active moiety is 40% lower than its single agent exposure (determined from GSK525762 80 mg cohort in BET115521 study), DL120 may be opened. The study team will carefully review PK and safety data from the DL80 and DL100 levels to determine if it is acceptable to open the DL120 dose level. If DL120 is opened, subjects in DL120 will begin dosing with GSK525762 at 120 mg and the approved dose of enzalutamide.

To further explore and identify the MTDs (and RP2Ds), the two most tolerable dose levels ~~Once a higher dose (either DL100 or DL120) and a lower dose (DL80) are determined to not exceed MTD, the dose expansion cohorts at the selected higher and lower doses~~ may ~~will~~ be initiated and ~~will be~~ randomized by prior lines of therapy (L2 or Lx). A total of 30 subjects each may ~~will~~ be enrolled into both cohorts, and approximately10 enrolled subjects will be L2 and 20 subjects will be Lx (Figure 4). 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.

Figure 4



Section 4.2.1 – Treatments Arms and Duration

Rationale for Change:

Revisions to clarify previous language and add flexible language. Replacement of word 'BET' in this section with 'GSK525762'.

Previous text:

This study will consist of dose escalation and dose expansion cohorts. A mTPI design will be followed during dose escalation to establish safe DLs to move to dose escalation. Subjects who have failed prior abiraterone/enzalutamide-treatment both as L2 as well as Lx will be enrolled to either of the following arms:

- Forced randomization of subjects that are abiraterone-refractory or resistant from L2 and Lx to DL60 and DL80 with 1/3 of the subjects from L2 and 2/3 of the subjects from Lx: - GSK525762 + abiraterone/prednisone (Arm A).
- Forced randomization of subjects that are enzalutamide-refractory or resistant from L2 and Lx to low and high dose expansion cohorts with 1/3 of the subjects from L2 and 2/3 of the subjects from Lx:- GSK525762 at RP2D+ enzalutamide (Arm B)

Revised text:

… This study will consist of dose escalation and dose expansion cohorts. A mTPI design will be followed during dose escalation to establish safe DLs to move to dose expansion~~escalation~~. During dose expansion, s~~S~~ubjects who have failed prior abiraterone/enzalutamide-treatment both as L2 as well as Lx will be enrolled to either of the following arms:

- Forced randomization of subjects that are abiraterone-refractory or resistant from L2 and Lx to the two most tolerable dose level cohorts ~~DL60 and DL80~~ with 1/3 of the subjects from L2 and 2/3 of the subjects from Lx: - GSK525762 + abiraterone/prednisone (Arm A).
- Forced randomization of subjects that are enzalutamide-refractory or resistant from L2 and Lx to the two most tolerable ~~low and high dose expansion~~dose level cohorts with 1/3 of the subjects from L2 and 2/3 of the subjects from Lx:- GSK525762 at RP2D+ enzalutamide (Arm B)

Section 4.2.2.1 – Planned Dose Levels

Rationale for Change:

Revisions to clarify previous language and add flexible language.

Previous text:

GSK525762 as a single agent is being investigated at the highest dose of 80 mg (amorphous tablet)/ 75 mg (besylate tablet) once daily (Recommended Part 2 Dose, RP2D) in the expansion cohorts of the first time in human solid tumor study (BET115521). All doses of GSK525762 refer to the besylate tablet formulation. For Arm A, projected dose levels of GSK525762 are 60 mg and 80 mg administered once daily.

For Arm B, projected dose levels of GSK525762 are 80 mg, and 100 mg administered once daily. A dose of 120 mg may be evaluated in combination with enzalutamide based on emerging PK and safety data.

Projected dose levels of abiraterone and enzalutamide are 1000 mg and 160 mg respectively, administered once daily. Additional doses and schedules may be explored based on emerging safety, PK, and PD data. No doses will be explored beyond 1000 mg abiraterone or 160 mg enzalutamide, these doses that are considered to be the Maximum Feasible Dose (MFD), unless emerging PK data demonstrate reduced exposure of either drug in combination compared to single agent. As determined from pre-clinical studies, the maximum clinical dose of GSK525762 will not exceed 200 mg. Any GSK525762 dose above 120 mg would require regulatory authority review and approval.

Revised text:

GSK525762 as a single agent was~~is being~~ investigated at the highest dose of 80 mg (amorphous tablet)/ 75 mg (besylate tablet) once daily (Recommended Phase~~art~~ 2 Dose, RP2D) in the expansion cohorts of the first time in human solid tumor study (BET115521). All doses of GSK525762 refer to the besylate tablet formulation. For Arm A, projected dose levels of GSK525762 are 60 mg and 80 mg administered once daily. 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.

For Arm B, projected dose levels of GSK525762 are 80 mg, and 100 mg administered once daily. A dose of 120 mg may be evaluated in combination with enzalutamide based on emerging PK and safety data. 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 DL80 exceeds the maximum permitted toxicity rate, then an alternate/intermittent dosing at 80 mg dose level (DL80 ALT) and/or a lower daily dose level (DL-1, 60 mg) may be evaluated.

Projected dose levels of abiraterone and enzalutamide are 1000 mg and 160 mg respectively, administered once daily. ~~Additional doses and schedules may be explored based on emerging safety, PK, and PD data.~~ No doses will be explored beyond 1000 mg abiraterone or 160 mg enzalutamide, these doses that are considered to be the Maximum Feasible Dose (MFD), unless emerging PK data demonstrate reduced exposure of either drug in combination compared to single agent. As determined from pre-clinical studies, the maximum clinical dose of GSK525762 will not exceed 200 mg. Any GSK525762 dose above 120 mg would require regulatory authority review and approval.

Section 4.2.2.6 – Alternative Dosing Schedules

Rationale for Change:

Revisions to clarify previous language.

Previous text:

…Schedules that incorporate a recovery period may be explored (e.g., 2 weeks on, 1 week off). This approach will be considered if the safety and PK data suggest that a therapeutic exposure cannot be achieved using the initial schedule without excessive toxicity. The starting dose for the alternate schedule will be the highest completed dose level with the initial schedule. Escalation can then proceed as described in Section 4.2.2….

Revised text:

…Schedules that incorporate a recovery period may be explored (e.g., 2 weeks on, 1 week off). This approach will be considered if the safety and PK data suggest that a therapeutic exposure cannot be achieved using the initial schedule without excessive toxicity. The starting dose for the alternate schedule will be no ~~the~~ higher~~st~~ than the maximum tolerated or completed dose level with the initial schedule. Escalation can then proceed as described in Section 4.2.2….

Section 4.4.1 – Type and Number of Subjects

Rationale for Change:

Addition of statement to clarify enrolment only would be used if 1 dose level cohort opened in dose expansion.

Previous text:

All subjects with a histologically-confirmed diagnosis of CRPC will be enrolled. 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). The total number of subjects required will depend upon the number of escalation steps required to identify the MTD(s). Once safe DL(s) are identified, the dose expansion phase will open and subjects with a histologically-confirmed diagnosis of CRPC will be randomized based on prior lines of therapy (L2 or Lx). For both Arms, each dose level cohort may enroll or randomize up to 30 subjects. Subjects from both dose escalation and dose expansion may be combined to reach 30 subjects.

Revised text:

All subjects with a histologically-confirmed diagnosis of CRPC will be enrolled. 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). The total number of subjects required will depend upon the number of escalation steps required to identify the MTD(s). Once safe DL(s) are identified, the dose expansion phase will open and subjects with a histologically-confirmed diagnosis of CRPC will be randomized based on prior lines of therapy (L2 or Lx). For both Arms, each dose level cohort may enroll or randomize up to 30 subjects. Subjects from both dose escalation and dose expansion may be combined to reach 30 subjects. If only one DL is opened for dose expansion, subjects will continue to be enrolled and their prior line of therapy (L2 or Lx) will be collected, but subjects will not be randomized.

Section 4.4.2 – Dose Selection

Rationale for Change:

Revisions to clarify previous language and add flexible language.

Previous text:

For Arm A, two dose combinations (DL60 and DL80) will be carried forward into expansion cohorts. However, for Arm B, the specific doses chosen will be based upon data from dose escalation. Two safe dose combinations will be carried forward into dose expansion cohorts.

Revised text:

For both Arms~~A~~, it is anticipated that the two most tolerable dose level ~~dose~~ combinations per arm~~(DL60 and DL80)~~ will be carried forward into expansion cohorts. If data warrants, only one dose level combination may be carried into dose expansion. ~~However, for Arm B, the specific doses chosen will be based upon data from dose escalation. Two safe dose combinations will be carried forward into dose expansion cohorts.~~

Section 4.4.3 – Statistical Design

Rationale for Change:

Revisions to add and clarify language regarding statistical analysis.

Previous text:

... Inference stemming from the Bayesian probabilities of efficacy in subjects harboring mCRPC are intended to inform decision making. Actual decisions will depend on the totality of the efficacy and safety data. The decision to terminate a cohort will not depend solely on the results of the statistical model but will take all factors into account, including the results of the model, safety, tolerability, PK, and PD data. In some cases, the enrolment for a cohort won't stop even if the model suggests a low likelihood of clinical activity in that combination.

Revised text:

... Inference stemming from the Bayesian probabilities of efficacy and tolerability in subjects harboring mCRPC are intended to inform decision making. Actual decisions will depend on the totality of the efficacy and safety data. The decision to terminate a cohort will not depend solely on the results of the statistical model but will take all factors into account, including the results of the model, additional efficacy parameters, safety, tolerability, PK, and PD data. In some cases, the enrolment for a cohort won't stop even if the model suggests a low likelihood of ~~clinical activity~~ clinically meaningful utility score in that combination.

Section 4.5 – Design Justification

Rationale for Change:

Revisions to clarify previous language and add flexible language.

Previous text:

Dose escalation will establish whether the combination of GSK525762 and abiraterone/enzalutamide are safe in two targeted dose levels for abiraterone or up to 3 targeted dose levels for enzalutamide. For dose expansion with enzalutamide, only 2 dose levels will be taken forward, with the 80 mg the targeted 'low' dose combination. The targeted 'high' dose combination will either be the 100 mg or 120 mg dose level based on the emerging data from the dose escalation part. If any dose level requires de-escalation to DL-1, further evaluation will be conducted by the study team to determine if 2 dose levels will be required per Arm during dose expansion.

By taking forward two doses into dose expansion, the study may be able to determine the ideal dose level in combination with abiraterone/enzalutamide that can be defined as the RP2D for each combination. To further establish a potential signal in 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.

Revised text:

Dose escalation will establish whether the combination of GSK525762 and abiraterone/enzalutamide are safe in ~~two~~ targeted dose levels for abiraterone or ~~up to 3~~ targeted dose levels for enzalutamide. For each arm, up to ~~dose expansion with enzalutamide, only~~ 2 dose levels will be taken forward, with a lower and higher GSK525762 dose, either as a continuous or intermittent dose administration. ~~, with the 80 mg the targeted 'low' dose combination. The targeted 'high' dose combination will either be the 100 mg or 120 mg dose level based on the emerging data from the dose escalation part. If any dose level requires de-escalation to DL-1,~~ F~~f~~urther evaluation will be conducted by the study team to determine if only 1 ~~2~~ dose level~~s~~ will be required per either Arm during dose expansion.

By taking forward up to two doses per arm into dose expansion, the study may be able to determine the ideal dose level in combination with abiraterone/enzalutamide that can be defined as the RP2D for each combination. To further establish a potential signal in 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.

Section 4.6.2. – Starting Doses GSK525762

Rationale for Change:

Update to language due to updated data.

Previous text:

A Phase I/II study (BET115521) with GSK525762 (as a single agent) is currently underway in subjects with advanced solid tumors, including CRPC. Doses of 2 to 100 mg once daily and doses of 20 mg, and 30 mg BID have been 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_05, 2016], 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.

Revised text:

A Phase I/II study (BET115521) with GSK525762 (as a single agent) was conducted~~is currently underway~~ in subjects with advanced solid tumors, including CRPC. Doses of 2 to 100 mg once daily and doses of 20 mg, ~~and~~ 30 mg and 40 mg BID were~~have been~~ 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~~6~~], 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.

Section 4.6.3. – Overlapping Toxicities

Rationale for Change:

Update to language due to additional data.

Previous text:

Summaries of findings from both clinical and non-clinical studies conducted with GSK525762 can be found in the Investigator Brochure. GSK525762 data provided in Section 4.6.3 reflects study treatment related AEs across all dose levels administered in the single-agent BET115521 solid tumor study as described in the Investigator's Brochure [GlaxoSmithKline Document Number 2011N113741_05]. The data cut-off date was 27 Jan 2016. Summaries of findings from both clinical and non-clinical studies conducted with enzalutamide/abiraterone can be found in the Food and Drug Administration (FDA) package insert. The following section outlines the risk assessment and mitigation strategy for this protocol

Revised text:

Summaries of findings from both clinical and non-clinical studies conducted with GSK525762 can be found in the Investigator Brochure. GSK525762 data provided in Section 4.6.3 reflects study treatment related AEs across all dose levels administered in the single-agent BET115521 solid tumor study as described in the Investigator's Brochure [GlaxoSmithKline Document Number 2011N113741_07~~5~~, 2018]. The data cut-off date was 29 Jan 2018~~27 Jan 2016~~. Summaries of findings from both clinical and non-clinical studies conducted with enzalutamide/abiraterone can be found in the Food and Drug Administration (FDA) package insert. The following section outlines the risk assessment and mitigation strategy for this protocol

Section 4.6.3.1.1. – Gastrointestinal Safety Findings

Rationale for Change:

Update to language due to additional data.

Previous text:

GSK525762: Gastrointestinal effects were frequently the dose-limiting toxicities in non-clinical animal studies of GSK525762. Dogs and rats treated with repeated doses of GSK525762 experienced reduced body weight, ulceration/inflammation of the gastrointestinal (GI) tract, and abnormal feces. In study BET115521, drug-related gastrointestinal events were reported, as well. Drug-related nausea was reported in 29% of subjects, dysgeusia was reported in 19%, decreased appetite was described in 17%,

and diarrhea was reported in 16% of subjects. Gastrointestinal toxicity was predominantly Grades 1 and 2; 3% of subjects reported Grade 3 nausea and 1% of subjects reported Grade 3 diarrhea. No Grade 4 gastrointestinal effects were observed.

Revised text:

GSK525762: Gastrointestinal effects were frequently the dose-limiting toxicities in non-clinical animal studies of GSK525762. Dogs~~and~~ rats and mice treated with repeated doses of GSK525762 experienced reduced body weight, ulceration/inflammation of the gastrointestinal (GI) tract, and abnormal feces. In study BET115521, drug-related GI ~~gastrointestinal~~ events were reported, as well. Drug-related nausea was reported in 41~~29~~% ~~of subjects~~, decreased appetite was reported in 36%, diarrhea was reported in 32%, dysgeusia was reported in 30~~19~~%, ~~decreased appetite was described in 17%, and diarrhea was reported in 16%~~ and vomiting was reported in 27% of subjects. Gastrointestinal toxicity was predominantly Grades 1 and 2; 5~~3~~% of subjects reported Grade 3 nausea, 4% reported Grade 3 decreased appetite, 3% reported Grade 3 vomiting, and 2% of subjects reported Grade 3 diarrhea. ~~and 1% of subjects reported Grade 3 diarrhea.~~ No Grade 4 GI~~gastrointestinal~~ effects were observed.

Section 4.6.3.1.2. – Hepatic Safety Findings

Rationale for Change:

Update to language due to additional data.

Previous text:

GSK525762: In non-clinical animal studies, non-adverse liver changes were observed in rats and dogs. Increased gall bladder vacuolation and; decreased cytoplasmic rarefaction in the liver was evident in dogs dosed at ≥1 mg/kg/day for 28 days. Necrosis was observed in one rat at 30 mg/kg/day in the 4 week study. In the BET115521 clinical trial, liver effects have been noted. Importantly, these effects appear isolated to the higher doses, and none have resulted in a pre-designated "liver event". At doses of 30 mg and below, no liver toxicity has been identified; one subject experienced Grade 3 hyperbilirubinemia but this was attributed by the investigator to the presence of extensive hepatic metastases and consequent liver dysfunction. Hyperbilirubinemia has been observed at 40 mg total daily dose and above in the solid tumor and hematologic malignancy studies. Drug related elevated blood bilirubin was reported in 13%, aspartate aminotransferase (AST) elevation was reported in 4%, alanine aminotransferase (ALT) elevation was reported in 4% of subjects. All drug related hepatic toxicities were predominantly Grades 1 and 2; 4% of subjects reported Grade 3 blood bilirubin increased and 1% of subjects reported Grade 3 AST increase. There were no Grade 3 ALT increases noted and no Grade 4 drug related hepatic effects were observed.

Revised text:

GSK525762: In non-clinical animal studies, non-adverse liver changes were observed in rats, mice and dogs including increases in bilirubin levels in rats, increased bile acids in rats and mice and transient, reversible increased in AST and/or ALT in rats and dogs. Hepatocellular necrosis was observed in a single rat at a non-tolerated dose. ~~Increased gall bladder vacuolation and; decreased cytoplasmic rarefaction in the liver was evident in dogs dosed at ≥1 mg/kg/day for 28 days. Necrosis was observed in one rat at 30 mg/kg/day in the 4 week study.~~ In the BET115521 clinical trial, liver effects have been

noted. Cases of liver events meeting the definition of severe liver injury based on liver chemistries (ALT ≥3X ULN and Bilirubin ≥2X ULN) have been reported in study BET115521. Additional complicating factors were reported for these cases (e.g. liver metastasis and sepsis) with liver enzymes trending towards normal levels upon stopping GSK525762. ~~Importantly, these effects appear isolated to the higher doses, and none have resulted in a pre-designated "liver event". At doses of 30 mg and below, no liver toxicity has been identified; one subject experienced Grade 3 hyperbilirubinemia but this was attributed by the investigator to the presence of extensive hepatic metastases and consequent liver dysfunction. Hyperbilirubinemia has been observed at 40 mg total daily dose and above in the solid tumor and hematologic malignancy studies.~~ Drug related elevated blood bilirubin was reported in 24~~13~~%, aspartate aminotransferase (AST) elevation was reported in 4~~1~~1%, and alanine aminotransferase (ALT) elevation was reported in 8~~4~~% of subjects. These~~All~~ drug related hepatic toxicities were predominantly Grades 1 and 2; 7~~4~~% ~~of subjects~~ reported Grade 3 and <1% reported Grade 4 blood bilirubin increased and 2% ~~and 1%~~ of subjects reported Grade 3 AST increase. There were no Grade 4~~3~~ ALT increases noted ~~and no Grade 4 drug related hepatic effects were observed~~.

Section 4.6.3.1.3. – Hematopoietic Safety Findings

Rationale for Change:

Update to language due to additional data.

Previous text:

GSK525762: In non-clinical studies of GSK525762, lymphoid / hematologic toxicity was observed in rats and dogs and the effects contributed to the definition of severely toxic repeat dose in rats (30 mg/kg). The effects manifested as hypocellularity in bone marrow, thymus, spleen and lymph nodes; decreased spleen and thymic weight; mild hemolysis; decreased white cell /lymphocyte count and variable and inconsistent changes in multiple red blood cells parameters and reticulocyte counts.

In the BET115521 clinical trial, thrombocytopenia has been observed in subjects with solid tumors mainly at doses of 60 mg and above. Forty one percent (41%) of subjects reported thrombocytopenia of any grade, and 24% of subjects reported Grade 3-4 thrombocytopenia. Thrombocytopenia was only noted after more than a week of continuous dosing, and platelet counts recovered after cessation of the drug. Anemia was reported in 11% of subjects, and 1% of subjects reported Grade 3 anemia.

Revised text:

GSK525762: In non-clinical studies of GSK525762, lymphoid / hematologic toxicity was observed in rats, mice and dogs and the effects contributed to the definition of severely toxic repeat dose in rats (30 mg/kg). The effects manifested as hypocellularity in bone marrow, thymus, spleen and lymph nodes; decreased spleen and thymic weight; mild hemolysis (rat); decreased white cell /lymphocyte/platelet count and variable and inconsistent changes in multiple red blood cells parameters and reticulocyte counts. Effects were generally reversible but minimal bone marrow cellularity was still evident in rats following an off dose period.

In the BET115521 clinical trial, thrombocytopenia has been observed in subjects with solid tumors mainly at doses of 60 mg and above. ~~Forty one percent (41%) of subjects~~

~~reported thrombocytopenia of any grade, and 24% of subjects reported Grade 3-4 thrombocytopenia.~~ Thrombocytopenia was only noted after more than a week of continuous dosing, and platelet counts recovered after cessation of the drug. Drug related thrombocytopenia was reported in 59%, anemia was reported in 29%, international normalized ratio increased was reported in 14%, prothrombin time prolonged in 12% and coagulation factor VII level decreased in 10% of subjects. These AEs were mainly Grade 1 or 2; with Grade 3 thrombocytopenia reported in 22%, Grade 3 anemia reported in 12% and Grade 3 factor VII decrease in 4% of subjects. Grade 4 thromobocytopenia was reported in 16%, anaemia in 1% and factor VII decrease in 4% of subjects. ~~Anemia was reported in 11% of subjects, and 1% of subjects reported Grade 3 anemia.~~

Mild to severe hemorrhagic events have been observed during the use of GSK525762, primarily during occurrences of moderate to severe thrombocytopenia. Most events have been associated with confounding factors beyond thrombocytopenia such as disease under study, and/or with metastases to affected areas, low molecular weight heparin use and previous radiation. There have been SAEs noted of decrease in Coagulation Factor VII. Refer to IB for additional details [GlaxoSmithKline Document Number 2011N113741_07, 2018].

Section 4.6.3.1.4. – General Toxicity Findings

Rationale for Change:

Update to language due to additional data.

Previous text:

GSK525762: In the BET115521 study, 16% of subjects reported fatigue and 9% reported asthenia. These effects were all Grade 1 or 2.

Revised text:

GSK525762: In the BET115521 study, 25~~16~~% of subjects reported fatigue and 24~~9~~% reported asthenia. Most of these AEs were Grade 1 or 2; with Grade 3 asthenia reported in 9% and Grade 3 fatigue in 3% of subjects. No Grade 4 asthenia/fatigue AEs were reported. ~~These effects were all Grade 1 or 2.~~

Section 4.6.4.1. – Cardiovascular Safety Findings

Rationale for Change:

Update to language due to additional data.

Previous text:

GSK525762:

…In the BET115521 and BET116183 clinical trials, evaluation of cardiac safety data from subjects treated up to the 100 mg once daily cohort by the cut-off date of May 15, 2015 demonstrated no significant QTc prolongation after single and repeat dose administration. Full analysis of cardiac safety data will be performed at the end of dose escalation in the BET115521 study.

Monitoring and Management: Subjects will be monitored closely for changes in QTc with triplicate 12-lead ECG and for elevations in plasma troponin. Safety ECGs will be performed at the time points specified in Time and Events tables (Section 7.1) using a

standard 12-lead ECG machine that automatically calculates the heart rate (HR) and measures PR, QRS, QT and QTcF intervals. The mean from triplicate ECGs will be evaluated at each time point. Safety ECGs will be reviewed by the investigator on an ongoing basis for safety purposes. Dosing should not begin until the safety ECG has been reviewed and no significant abnormalities have been detected.

Revised text:

GSK525762:

…An internal safety review of categorical analysis of QTc increase (and decrease) from baseline of 271 subjects dosed up to 100 mg in ~~In~~ the BET115521 and up to 120 mg in the BET116183 clinical trials demonstrated a clinically negligible effect on QTc. Based on this analysis, the entry and stopping criteria have been modified.~~, evaluation of cardiac safety data from subjects treated up to the 100 mg once daily cohort by the cut-off date of May 15, 2015 demonstrated no significant QTc prolongation after single and repeat dose administration. Full analysis of cardiac safety data will be performed at the end of dose escalation in the BET115521 study.~~

Monitoring and Management: Subjects will be monitored closely for changes in QTc with ~~triplicate~~ 12-lead ECG and for elevations in plasma troponin. Safety ECGs will be performed at the time points specified in Time and Events tables (Section 7.1) using a standard 12-lead ECG machine that automatically calculates the heart rate (HR) and measures PR, QRS, QT and QTcF intervals. As clinically indicated, ~~T~~the mean from triplicate ECGs will be evaluated. ~~at each time point~~. Safety ECGs will be reviewed by the investigator on an ongoing basis for safety purposes. Dosing should not begin until the safety ECG has been reviewed and no significant abnormalities have been detected.

Section 5.1 – Inclusion Criteria

Rationale for Change:

Revisions to wording of specific criteria to correct or clarify original wording and revise based on investigator feedback/internal decisions. Only the criteria which has been affected will be listed in both Previous and Revised sections.

Previous text:

3. Histologically confirmed adenocarcinoma of the prostate:

   b. Screening biopsy can be waived if patient had a recent biopsy after failure of ADT therapy (within 30 days) and the biopsy sample is secured to be sent as screening biopsy for this study.

4. Surgically or medically castrated, with testosterone levels of ≤ 50 ng/dL (<2.0 nM). If the patient is being treated with LHRH agonists/antagonists (patient who have not undergone orchiectomy) this therapy must have been initiated at least 4 weeks prior to Cycle 1 Day 1 and must be continued throughout the study.

5. Subjects must have failed prior therapy with abiraterone, enzalutamide, or both

   a. Has completed at least 12 weeks of prior continuous therapy with abiraterone or enzalutamide

b. Has not been without abiraterone or enzalutamide treatment for >30 days prior to initiation of study treatment

6. One to two line(s) of prior taxane-based chemotherapy allowed. If docetaxel chemotherapy is used more than once, this will be considered as one regimen.

7. Documented prostate cancer progression as assessed by the investigator with one of the following:

   a. PSA progression defined by a minimum of 3 rising PSA levels with an interval of ≥1 week between each determination. The PSA value at screening must be ≥5 ug/L (5 ng/mL) if PSA is the only indication of progression; subjects on systemic glucocorticoids for control of symptoms must have documented PSA progression by PCWG3 while on systemic glucocorticoids prior to commencing Cycle 1 Day 1 treatment.

   b. Radiographic progression of soft tissue disease by PCWG3-modified RECIST 1.1 criteria or bone metastasis with 2 or more documented new bone lesions on a bone scan with or without PSA progression

11. Adequate organ function as defined in Table 1:

System	Laboratory Values
Cardiac	
Ejection fraction	≥ lower limit of normal (LLN) by echocardiogram or multigated acquisition scan (MUGA) and minimum of 50% LVEF

12. Male subject with a female partner of childbearing potential or pregnant must agree to use two acceptable methods of contraception from time of first dose of study treatment until 4 months after the last dose of study treatments.

Revised text:

3. Histologically confirmed adenocarcinoma of the prostate:

   b. Screening biopsy can be waived if patient had a recent biopsy after failure of ~~ADT therapy~~ the most recent therapy (within 30 days) and the biopsy sample is secured to be sent as screening biopsy for this study.

4. Surgically or medically castrated, with testosterone levels of ≤ 50 ng/dL (<2.0 nM). If the patient is being treated with LHRH agonists/antagonists (patient who have not undergone orchiectomy) this therapy must have been initiated at least 4 weeks prior to Week 1 ~~Cycle 1~~ Day 1 and must be continued throughout the study.

5. Subjects must have failed prior therapy with abiraterone, enzalutamide, or both

   a. Has completed at least 12 weeks of prior continuous therapy with abiraterone or enzalutamide in any prior line

   ~~b. Has not been without abiraterone or enzalutamide treatment for >30 days prior to initiation of study treatment~~

6. One to two line(s) of prior taxane-based chemotherapy allowed. If docetaxel chemotherapy is used more than once, this will be considered as one regimen. Subjects who have not received prior chemotherapy in any setting will qualify for study if they are ineligible for or refuse chemotherapy.

7. Documented prostate cancer progression as assessed by the investigator with one of the following:

   a. PSA progression defined by a minimum of 3 rising PSA levels with an interval of ≥1 week between each determination. The PSA value at screening must be ≥5 ug/L (5 ng/mL) if PSA is the only indication of progression; subjects on systemic glucocorticoids for control of symptoms must have documented PSA progression by PCWG3 while on systemic glucocorticoids prior to commencing Week~~Cycle~~ 1 Day 1 treatment.

   b. Radiographic progression of soft tissue disease by PCWG3-modified RECIST 1.1 criteria or bone metastasis with 2 or more documented new bone lesions on a bone scan/ CT scan with or without PSA progression

11. Adequate organ function as defined in Table 1:

System	Laboratory Values
Cardiac	
Ejection fraction	≥ lower limit of normal (LLN) by echocardiogram or multigated acquisition scan (MUGA) and minimum of 50% LVEF
Troponin (I or T)	≤ ULN

12. ~~Male subject with a female partner of childbearing potential or pregnant must agree to use two acceptable methods of contraception from time of first dose of study treatment until 4 months after the last dose of study treatments (Section 6.10.2).~~ Male Participants: Contraceptive use by men or female partner should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Male participants are eligible to participate if they agree to the following during the intervention period and for at least 16 weeks after the last dose of study treatment:

- Refrain from donating sperm

PLUS either:

- 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.

Section 5.2 - Exclusion Criteria

Rationale for Change:

Revisions to wording of specific criteria to correct or clarify original wording and revise based on investigator feedback/internal decisions. Only the criteria which has been affected will be listed in both Previous and Revised sections.

Previous text:

1. Surgery or local prostatic intervention (excluding a prostatic biopsy) less than 28 days of Cycle 1 Day 1.

5. Cardiac abnormalities as evidenced by any of the following:

    a. Baseline QT duration corrected for heart rate by Fridericia's formula (QTcF) interval ≥450 msec

8. Concurrent use of high dose aspirin (doses up to 81 mg oral dose daily allowed) 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

12. History of seizure or any condition that may predispose subject to seizure (e.g., prior cortical stroke or significant brain trauma).

15. Subjects who have experienced a seizure or seizures within 6 months of study treatment or who are currently being treated with cytochrome P450 enzyme inducing anti-epileptic drugs for seizures (use of anti-epileptic drugs to control pain is allowed in subjects not suffering from seizures unless drug is excluded due to CYP3A4 induction - phenytoin, carbamazepine, phenobarbital).

16. Current use of a prohibited medication or planned use of any forbidden medications during treatment with GSK525762 and abiraterone/enzalutamide. This includes medications with significant risk of Torsades de pointes as well as those that are potent inducers or inhibitors of CYP3A4 enzymes or strong inhibitors of CYP2C8.

20. Initiating bisphosphonate or denosumab therapy or adjusting dose/regimen within 3 months prior to Cycle 1 Day 1. Subjects on a stable bisphosphonate or denosumab therapy are eligible and may continue.

Revised text:

1. Surgery or local prostatic intervention (excluding a prostatic biopsy) less than 28 days of Week~~Cycle~~ 1 Day 1.

5. Cardiac abnormalities as evidenced by any of the following:

    a. Baseline QT duration corrected for heart rate by Fridericia's formula (QTcF) interval ≥48~~5~~0 msec

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

12. History of seizure within 6 months of first dose of study treatment or any condition that may predispose subject to seizure (e.g., prior cortical stroke or significant brain trauma) or who are currently being treated with cytochrome P450 enzyme inducing anti-epileptic drugs for seizures (use of anti-epileptic drugs to control pain is allowed in subjects not suffering from seizures unless drug is excluded due to CYP3A4 induction - phenytoin, carbamazepine, phenobarbital).

~~15. Subjects who have experienced a seizure or seizures within 6 months of study treatment or who are currently being treated with cytochrome P450 enzyme inducing anti-epileptic drugs for seizures (use of anti-epileptic drugs to control pain is allowed in subjects not suffering from seizures unless drug is excluded due to CYP3A4 induction - phenytoin, carbamazepine, phenobarbital).~~

15. Current use of a prohibited medication or planned use of any forbidden medications during treatment with GSK525762 and abiraterone/enzalutamide. This includes medications ~~with significant risk of Torsades de pointes as well as those~~ that are potent inducers or inhibitors of CYP3A4 enzymes or strong inhibitors of CYP2C8.

19. Initiating bisphosphonate or denosumab therapy or adjusting dose/regimen within 3 months prior to Week~~Cycle~~ 1 Day 1. Subjects on a stable bisphosphonate or denosumab therapy are eligible and may continue.

Section 5.4.2. – QTc Stopping Criteria

Rationale for Change:

Updated wording based on revised recommendations by internal safety panel.

Previous text:

… Study treatments will be withheld if either of the following occurs:

- QTcF interval ≥500 msec
- QTcF interval increase from baseline ≥60 msec…

Revised text:

… Study treatments will be withheld if either of the following occurs:

- QTcF interval ≥500 msec AND ≥60 msec change from baseline
- QTcF interval ≥530 msec AND ~~increase from baseline ≥~~≤60 msec change from baseline…

Section 5.5. – Subject and Study Completion

Rationale for Change:

Addition of wording to clarify analysis based on evaluable subject population.

Previous text:

Subjects who have not died, and are no longer being followed for survival are considered to have discontinued the study. The End of Study eCRF should only be completed when a subject is no longer being followed. The study will be considered completed for purposes of a final analysis when 70% of subjects enrolled have progressed or died. If available,

subjects continuing on GSK525762 at the time of final analysis may be offered the option to continue it through another mechanism (eg, in a rollover trial).

Revised text:

Subjects who have not died, and are no longer being followed for survival are considered to have discontinued the study. The End of Study eCRF should only be completed when a subject is no longer being followed. The study will be considered completed for purposes of a final analysis when 70% of evaluable subjects enrolled have progressed or died. If available, subjects continuing on GSK525762 at the time of final analysis may be offered the option to continue it through another mechanism (eg, in a rollover trial).

Section 6.1. – Investigational Product and Other Study Treatment

Rationale for Change:

Addition of new formulation of abiraterone acetate and clarification of wording for GSK525762 tablets.

Previous text:

Investigational Product					
Product name:	GSK525762 Besylate Tablets			Abiraterone acetate	Enzalutamide
Unit dose strength(s)/Dosage level(s):	5 mg[a]	25 mg[a]	20 mg[a]	250 mg	40 mg
Dosage form	Tablet	Tablet	Tablet	Tablet	Tablet
Manufacturer	GSK	GSK	GSK	Janssen	Astellas
Physical description:	White to slightly colored, round, biconvex tablets with no markings, film-coated tablet		Beige, round, biconvex tablets with no markings, film-coated	White to off-white, oval tablets debossed with AA250 on one side	White to off-white oblong soft gelatin capsules imprinted in black ink with ENZ

Revised text:

Investigational Product						
Product name:	GSK525762 Besylate Tablets			Abiraterone acetate		Enzalutamide
Unit dose strength(s)/Dosage level(s):	5 mg[a]	25 mg[a]	20 mg[a]	250 mg	500 mg[b]	40 mg
Dosage form	Tablet	Tablet	Tablet	Tablet	Tablet	Tablet
Manufacturer	GSK	GSK	GSK	Janssen	Janssen	Astellas
Physical description:	White to slightly colored, round, biconvex tablets with no markings, film-coated tablet		~~Beige~~Yellowish-pink, round, biconvex tablets with no markings, film-coated	White to off-white, oval tablets debossed with AA250 on one side	Film-coated, purple oval tablets debossed with AA on one side and 500 on the other side	White to off-white oblong soft gelatin capsules imprinted in black ink with ENZ

b. The 500 mg tablet may be supplied dependent on the availability by Janssen. The use of 250 mg tablet formulation may be discontinued when 500 mg tablet is available

Section 6.2. – Treatment Assignment

Rationale for Change:

Revisions to clarify previous language and add flexible language.

Previous text:

…For Arm A, during the initial evaluation of DL60, approximately 3 to 10 subjects will be enrolled until it is determined that DL60 does not exceed the MTD. If DL60 exceeds the maximum permitted toxicity rate, then a lower dose level (DL-1, 40 mg) will be evaluated. If DL60 has been cleared in dose escalation, approximately 6 to 10 subjects will be enrolled in the DL80 cohort for evaluation of dose escalation. If DL80 cohort is opened, but exceeds the maximum permitted toxicity rate, then additional subjects will not be enrolled at DL80. Subjects enrolled during dose escalation will continue treatment and will not roll into dose expansion.

To further explore and identify the MTDs (and RP2Ds), the two most tolerable dose levels may be If DL60 and DL80 are cleared for DLT, eligible subjects will be randomized into DL60 and DL80 expansion cohorts and will be based on prior lines of therapy (L2 or Lx). A maximum of up to 30 subjects each (in addition to those enrolled in dose escalation) will be enrolled into each dose level cohort…

…During the initial evaluation of DL80, approximately 3 to 10 subjects will be enrolled until it is determined that DL80 does not exceed the MTD. If DL80 exceeds the maximum permitted toxicity rate, then a lower dose level (DL-1, 60 mg) will be evaluated. If DL80 has been cleared in dose escalation, approximately 3 to 10 subjects will be enrolled in the DL100 cohort until it is determined that DL100 does not exceed the MTD. If DL100 cohort is opened, but exceeds the maximum permitted toxicity rate, then additional subjects will not be enrolled at DL100.

An additional dose level, DL120, may be initiated after careful review of the PK and safety data from the DL80 and DL100 dose levels. If the DL120 cohort is opened, it will enrol approximately 3 to 10 subjects until it is determined whether DL120 does not exceed the MTD. Either DL100 or DL120 will be established as the 'high dose' and DL80 will be the 'low dose'. Regardless of which dose (DL100 or DL120) is selected as the 'high dose', a minimum of 6 subjects will be enrolled during initial evaluation prior to moving to dose expansion. Subjects enrolled during dose escalation will continue treatment and will not roll into dose expansion.

If the dose escalation DLT cohorts are cleared, eligible subjects will be randomized into DL80 and DL100 (or DL120), dose expansion cohorts will be based on prior lines of therapy (L2 or Lx). A maximum up to 30 subjects each (in addition to those enrolled in dose escalation) will be enrolled into each dose level cohort.

Revised text:

…For Arm A, during the initial evaluation of DL60, approximately 3 to 10 subjects will be enrolled until it is determined that DL60 does not exceed the MTD. ~~If DL60 exceeds the maximum permitted toxicity rate, then a lower dose level (DL-1, 40 mg) will be evaluated.~~ 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 schedule, 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 intermittent dosing at 60 mg dose level (DL60 ALT) and/or a lower daily dose level (DL-1, 40 mg) may be evaluated). If DL60 has been cleared in dose escalation, approximately 6 to 10 subjects will be enrolled in the DL80 cohort for evaluation of dose escalation. If any dose level~~DL80~~ cohort is opened, but exceeds the maximum permitted toxicity rate, then additional subjects will not be enrolled at that dose level~~DL80~~. Subjects enrolled during dose escalation will continue treatment and will not roll into dose expansion.

To further explore and identify the MTDs (and RP2Ds), the two most tolerable dose levels may be ~~If DL60 and DL80 are cleared for DLT, eligible subjects will be~~ randomized into ~~DL60 and DL80~~2 expansion cohorts and will be based on prior lines of therapy (L2 or Lx). A maximum of up to 30 subjects each (in addition to those enrolled in dose escalation) will be enrolled into each dose level cohort…

…During the initial evaluation of DL80, approximately 3 to 10 subjects will be enrolled until it is determined that DL80 does not exceed the MTD. ~~If DL80 exceeds the maximum permitted toxicity rate, then a lower dose level (DL-1, 60 mg) will be evaluated.~~ 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 schedule, either at a dose level where daily treatment may be intolerable or at a lower dose. For example, if DL80 exceeds the maximum permitted toxicity rate, then intermittent dosing at 80 mg dose level (DL80 ALT) and/or a lower daily dose level (DL-1, 60 mg) may be evaluated. If DL80 has been cleared in dose escalation, approximately 3 to 10 subjects will be enrolled in the DL100 cohort until it is determined that DL100 does not exceed the MTD. If any dose level cohort ~~DL100 cohort~~ is opened, but exceeds the maximum permitted toxicity rate, then additional subjects will not be enrolled at that dose level~~DL100~~.

An additional dose level, DL120, may be initiated after careful review of the PK and safety data from the DL80 and DL100 dose levels. If the DL120 cohort is opened, it will enrol approximately 3 to 10 subjects until it is determined whether DL120 does not exceed the MTD. ~~Either DL100 or DL120 will be established as the 'high dose' and DL80 will be the 'low dose'. Regardless of which dose (DL100 or DL120) is selected as the 'high dose', a minimum of 6 subjects will be enrolled during initial evaluation prior to moving to dose expansion.~~ Subjects enrolled during dose escalation will continue treatment and will not roll into dose expansion.

To further explore and identify the MTDs (and RP2Ds), the two most tolerable dose levels may be initiated ~~If the dose escalation DLT cohorts are cleared,~~ and eligible subjects may ~~will~~ be randomized ~~into DL80 and DL100 (or DL120), dose expansion cohorts will be based on~~ by prior lines of therapy (L2 or Lx). A maximum up to 30 subjects each (in addition to those enrolled in dose escalation) will be enrolled into each dose level cohort. If only one dose level is tolerable for dose expansion, subjects will be enrolled and not randomized.

Section 6.3. – Planned Dose Adjustments

Rationale for Change:

Additional language added regarding minimum GSK525762 dose.

Previous text:

….During any dose interruption of GSK525762, abiraterone or enzalutamide may be continued at the protocol dose unless dose interruption of these combination products is also required. If GSK525762 is permanently discontinued, subject must be discontinued from the abiraterone or enzalutamide treatment and withdrawn from the study.

Revised text:

Based on dose table (Table 6) and effect of enzalutamide on GSK525762, no dose level/schedule of less than 40 mg QD will be allowed for Arm B. If a subject is on an alternate dosing schedule and requires a de-escalation to 40 mg, then the subject must move to 40 mg QD.

….During any dose interruption of GSK525762, abiraterone or enzalutamide may be continued at the protocol dose unless dose interruption of these combination products is also required. If GSK525762 is permanently discontinued, subject must be discontinued from the abiraterone or enzalutamide treatment and withdrawn from the study.

Section 6.3.1. – Guidelines for Events of Special Interest

Rational for Change:

Removal of Section for consistency with other modifications in protocol and IB.

Previous text:

Guidelines for Events of Special Interest

Events of special interest are defined in Appendix 8 and the GSK525762 IB [GlaxoSmithKline Document Number 2011N113741_05]. The severity of adverse events (AEs) will be graded utilizing the National Cancer Institute- Common Toxicity Criteria for Adverse Events [NCI-CTCAE, version 4, 2009]. Guidelines for dose modifications

and interruptions for management of common toxicities associated with the study treatment(s) are provided in Appendix 2.

Revised text:

~~**Guidelines for Events of Special Interest**~~

~~Events of special interest are defined in Appendix 8 and the GSK525762 IB [GlaxoSmithKline Document Number 2011N113741_05]. The severity of adverse events (AEs) will be graded utilizing the National Cancer Institute- Common Toxicity Criteria for Adverse Events [NCI-CTCAE, version 4, 2009]. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment(s) are provided in Appendix 2.~~

Section 6.6. – Preparation/Handling/Storage/Accountability

Rationale for Change:

Revisions to language due to updated GSK525762 handling language.

Previous text:

Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

Revised text:

Limited exposure and precautionary action (e.g., wearing gloves, washing hands post exposure, etc.) should be taken by site staff dispensing GSK525762. ~~Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.~~ A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

Section 6.10.2. – Male Subjects

Rationale for Change:

Revisions to presentation of language. Removal of section as language moved to Inclusion Criteria and Appendix.

Previous text:

Subjects with female partners of child-bearing potential must use acceptable, highly effective forms of contraceptive methods (i.e., a failure rate of ≤1%) defined in Appendix 12 after the first dose of study treatment and until 4 months after the last dose of study drug (note that these requirements do not apply if female partners are not of child-bearing potential).

Female partner use of hormonal means of birth control such as oral contraceptives are NOT acceptable forms of birth control given that their efficacy has not been evaluated when given in combination with the investigational drugs.

In addition, male subjects whose partners are or become pregnant while on study medication must continue to use condoms for 4 months after stopping study medications.

Revised text:

~~Subjects with female partners of child-bearing potential must use acceptable, highly effective forms of contraceptive methods (i.e., a failure rate of ≤1%) defined in Appendix 12 after the first dose of study treatment and until 4 months after the last dose of study drug (note that these requirements do not apply if female partners are not of child-bearing potential).~~

~~Female partner use of hormonal means of birth control such as oral contraceptives are NOT acceptable forms of birth control given that their efficacy has not been evaluated when given in combination with the investigational drugs.~~

~~In addition, male subjects whose partners are or become pregnant while on study medication must continue to use condoms for 4 months after stopping study medications.~~

Section 6.11.2.1. – Prohibited Medications

Rationale for Change:

Revisions to language based on exclusion criteria revisions.

Previous text:

…Subjects may continue to use Aspirin, but doses are not allowed to be greater than 81 mg per day. The use of non-steroidal anti-inflammatory drugs (NSAIDs) will be excluded, except for when NSAIDs will provide benefit over other analgesics and then to be used with caution including concomitant use of proton pump inhibitors….

....Co-administration of the medications listed in Table 7 are prohibited for 5 half-lives (or at least 14 days, whichever is longer) prior to the first dose of study drug until discontinuation from the study drug due to unacceptable risk of Torsades de Pointes (with the exception of amiodarone, which is prohibited beginning 6 months prior to screening through discontinuation from the study. [However, there may be situations when the subject is on study and Advanced Cardiac Life Support (ACLS) requires the use of amiodarone, which should be used as per local clinical guidelines]).

These medications include (but are not limited to):

Table 7: Drugs with a Risk of Torsades de Pointes that are Prohibited

Revised text:

…Subjects may continue to use Aspirin, but doses are not allowed to be greater than 81 mg per day <u>(or 100 mg, as per country standards).</u> The use of non-steroidal anti-inflammatory drugs (NSAIDs) will be excluded, except for when NSAIDs will provide benefit over other analgesics and then to be used with caution including concomitant use of proton pump inhibitors….

....~~Co-administration of the medications listed in Table 7 are prohibited for 5 half-lives (or at least 14 days, whichever is longer) prior to the first dose of study drug until discontinuation from the study drug due to unacceptable risk of Torsades de Pointes (with the exception of amiodarone, which is prohibited beginning 6 months prior to screening through discontinuation from the study. [However, there may be situations when the~~

~~subject is on study and Advanced Cardiac Life Support (ACLS) requires the use of amiodarone, which should be used as per local clinical guidelines]).~~

~~These medications include (but are not limited to):~~

Table 7: Drugs with a Risk of Torsades de Pointes that are Prohibited

Removed Table.

Section 6.11.2.3. – Cautionary Medications

Rationale for Change:

Revisions to language based on exclusion criteria revisions and language based on safety panel review.

Previous text:

Subjects should minimize the use of medications which contain acetaminophen. Subjects should be informed of alternative medications. ….

… Co-administration of GSK525762 and the following medications requires extreme caution beginning 14 days prior to the first dose of study drug until discontinuation from the study due to an increased risk of Torsades de Pointes. These medications include (but are not limited to):

Table 8: Drugs with a Risk of Torsades de Pointes which are permitted for co-administration with Extreme Caution

After starting cautionary medications such as in Table 8, it is recommended that ECGs are implemented daily until the steady state of the new medication is reached. If there are ECG abnormalities, implement additional cardiotoxicity monitoring as addressed Appendix 2.

Revised text:

Subjects should minimize the use of medications which contain acetaminophen. ~~Subjects should be informed of alternative medications.~~ ….

… Co-administration of GSK525762 and <u>medications which may have an increased risk of Torsades de Pointes</u> ~~the following medications~~ requires extreme caution beginning 14 days prior to the first dose of study drug until discontinuation from the study. ~~, due to an increased risk of Torsades de Pointes.~~ <u>Please reference current list of medications at crediblemeds.org.</u> ~~These medications include (but are not limited to):~~

Table 8: Drugs with a Risk of Torsades de Pointes which are permitted for co-administration with Extreme Caution

Removed Table.

After starting cautionary medications such as <u>any listed in the referenced internet link</u>~~in Table 8~~, it is recommended that ECGs are implemented daily until the steady state of the new medication is reached. If there are ECG abnormalities, implement additional cardiotoxicity monitoring as addressed Appendix 2.

Section 7.1. – Time and Events Table

Rationale for Change:

Revisions and update to tables based on changes in other Sections. Addition of Week 6 Laboratory Tests due to internal safety panel recommendation. Revisions to footnotes where applicable due to changes in other Sections. Only Rows and affected footnotes are presented.

Previous text:

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 there after	
Safety														
12-lead ECGs (Triplicate)[6]	X		X	X	X		X		X	X	X		X	X
Echocardiogram or MUGA[8]	X		X							X	Weeks 13, 25 and 37		X	X
Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)														
Tumor biopsy[13]	X						One sample, collected 3-6h post-GSK525762 dose, between W3D1 and W4D1							X[14]
Biomarker Assessments														
CTC – ARV[17]			X							X	Week 9 only			X

2. Screening echocardiogram or MUGA scans should be completed within 35 days prior to the first dose of study drugs. Baseline imaging should be completed within 28 days prior to first dose of study drugs. All other assessments should be within 14 days prior to first dose of any study drugs.
6. Triplicate ECGs should be performed prior to dosing and evaluated for abnormality prior to administration of dose.
12. "PK" = serial PK days. Sample collections should be obtained at the following timepoints: Pre-dose, 30m ± 5m, 1h ± 10m, 3h ± 30m, 6 to 12 hours and 24 h± 2h but prior to dosing. "O" = sample collections to be obtained pre-dose, 0.5-1h post-dose, and an optional sample 4-12h post-dose. "X" = sample collections to be obtained pre-dose as well as 0.5-1h post-dose (note that routine PK is no longer required once the subject has been on study for 26 weeks). PK samples will be split to obtain PK samples for abiraterone and enzalutamide. Abiraterone PK samples will be collected at all PK time points in Week 1 and Week 3 and only at pre-dose at remaining PK visits. Enzalutamide PK samples will be collected at pre-dose for all PK visits. Refer to the SRM for further details. Once extensive PK sampling in Week 1 and Week 3 have been collected from at least 12 subjects for each dose and combination cohorts, PK sampling may be reduced for these visits.
13. Paired fresh biopsies must be provided pre- and post-dose at time points indicated. If it is not feasible to obtain a fresh biopsy, an archival sample must be provided. Fresh biopsies should be paired with plasma and whole blood samples for PK and circulating biomarkers collected as close as possible to biopsy (ideally within

1h). Subjects must have a platelet count of ≥75,000/mm3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy procedures. Refer to the SRM for further details

16. CTC-ENU: Whole blood samples will be obtained for CTC enumeration at Screening; pre-dose on W1D1 of the combination treatment period, W5D1, W9D1 and every 8 weeks for the first 6 months and thereafter every 12 weeks; and EOT.
17. CTC-ARV: Whole blood samples will be obtained for measuring AR-Vs at pre-dose on W1D1, W5D1, and W9D1 of the combination treatment period; and EOT. Based on emerging data, GSK may decide to discontinue the collection of these samples.

Table 8 Dose Escalation Time and Events, Laboratory Assessments

		Week 1		Week 2		Week 3		Week 4	Week 5	q2w	q4w	q4w	q12w	
	SCR	D1	D4	D1	D4	D1	D4	D1	D1	W7 and 11	W9 to W49	W49 and thereafter	W49 and thereafter	EOT
Clinical chemistry	X	X	X	X		X		X	X	X[2]	X	X[2]	X	X
Hematology	X	X	X	X	X	X	X	X	X	X[2]	X	X[2]	X	X
Liver chemistry	X	X	X	X	X	X	X	X	X	X[2]	X	X[2]	X	X
Coagulation	X	X	X	X		X		X	X	X[2]	X	X[2]	X	X
Thyroid stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4))	X								X		X		X	X

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	
Safety											
12-lead ECGs (Triplicate)[6]	X		X	X	X	X	X	X		X	X
Echocardiogram or MUGA[8]	X		X				X	Weeks 13, 25 and 37		X	X
Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)											
Tumor biopsy[13]	X				One sample, collected 3-6h post-GSK525762 dose, between W3D1 and W4D1						X[14]
Biomarker Assessments											
CTC – ARV[17]			X				X	Week 9 only			X

2. Screening echocardiogram or MUGA scans should be completed within 35 days prior to the first dose of study drugs. Baseline imaging should be completed within 28 days prior to first dose of study drugs. All other assessments should be within 14 days prior to first dose of any study drugs.
6. Triplicate ECGs should be performed prior to dosing and evaluated for abnormality prior to administration of dose.
12. "PK" = serial PK days. Sample collections should be obtained at the following timepoints: Pre-dose, 30m ± 5m, 1h ± 10m, 3h ± 30m, 6 to 12 hours and 24 h± 2h but prior to dosing. "O" = sample collections to be obtained pre-dose, 0.5-1h post-dose, and an optional sample 4-12h post-dose. "X" = sample collections to be obtained pre-dose as well as 0.5-1h post-dose (note that routine PK is no longer required once the subject has been on study for 26 weeks). PK samples will be split to obtain PK samples for abiraterone and enzalutamide. Abiraterone PK samples will be collected at all PK time points in Week 1 and Week 3 and only at pre-dose at remaining PK visits. Enzalutamide PK samples will be collected at pre-dose for all PK visits. Refer to the SRM for further details. Once extensive PK sampling in Week 1 and Week 3 have been collected from at least 12 subjects for each dose and combination cohorts, PK sampling may be reduced for these visits.
13. Paired fresh biopsies must be provided pre- and post-dose at time points indicated. If it is not feasible to obtain a fresh biopsy, an archival sample must be provided. Fresh biopsies should be paired with plasma and whole blood samples for PK and circulating biomarkers collected as close as possible to biopsy (ideally within 1h). Subjects must have a platelet count of ≥75,000/mm3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy procedures. Refer to the SRM for further details
16. CTC-ENU: Whole blood samples will be obtained for CTC enumeration at Screening; pre-dose on W1D1 of the combination treatment period, W5D1, W9D1 and every 8 weeks for the first 6 months and thereafter every 12 weeks; and EOT.
17. CTC-ARV: Whole blood samples will be obtained for measuring AR-Vs at pre-dose on W1D1, W5D1, and W9D1 of the combination treatment period; and EOT. Based on emerging data, GSK may decide to discontinue the collection of these samples.

Table 10 Dose Expansion Time and Events, Laboratory Assessments

	SCR	Week 1	Week 2	Week 3	Week 4	Week 5	q2w	q4w	q4w	q12w	EOT
		D1	D1	D1	D1	D1	W7 and 11	W9 to W49	W49 and thereafter	W49 and thereafter	
Clinical chemistry	X	X	X	X	X	X	X[2]	X	X[2]	X	X
Hematology	X	X	X	X	X	X	X[2]	X	X[2]	X	X
Liver chemistry	X	X	X	X	X	X	X[2]	X	X[2]	X	X
Coagulation	X	X	X	X	X	X	X[2]	X	X[2]	X	X
Thyroid (Thyroid stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4))	X					X		X		X	X

Revised text:

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	
Safety														
12-lead ECGs ~~(Triplicate)~~[6]	X		X	X	X		X		X	X	X		X	X
Echocardiogram or MUGA[8]	X		~~X~~							X	Weeks 13, 25 and 37		X	X
Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)														
Tumor biopsy[13]	X						One sample, collected 3-6h post-GSK525762 dose, between W3D1 and W4-5D1							X[14]
Biomarker Assessments														
CTC – ARV[17]			X							~~X~~	~~Week 9 only~~			~~X~~

3. Screening echocardiogram or MUGA scans should be completed within 35 days prior to the first dose of study drugs. ~~Baseline imaging should be completed within 28 days prior to first dose of study drugs~~. All other assessments should be within 28~~14~~ 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.
7. Triplicate ECG~~s~~ 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.
14. "PK" = serial PK days. Sample collections should be obtained at the following timepoints: Pre-dose, 30m ± 5m, 1h ± 10m, 3h ± 30m, 6 to 12 hours and 24 h± 2h but prior to dosing. "O" = sample collections to be obtained pre-dose, 0.5-1h post-dose, and an optional sample 4-12h post-dose. "X" = sample collections to be obtained

pre-dose as well as 0.5-1h post-dose (note that routine PK is no longer required once the subject has been on study for 26 weeks). PK samples will be split to obtain PK samples for abiraterone and enzalutamide. Abiraterone PK samples will be collected at all PK time points in Week 1 and Week 3 and only at pre-dose at remaining PK visits. Enzalutamide PK samples will be collected at pre-dose for all PK visits. Refer to the SRM for further details. For subjects in alternate dosing schedule, the Week 3 Day 1 extensive PK will need to occur between W2 Day 4 and W2 Day 7 prior to their scheduled dose interruption. For any PK timepoint, subjects should have received GS525762 for at least 7 days prior to their scheduled PK draws. This may require the subject to return earlier than any planned interruption of dosing. Once extensive PK sampling in Week 1 and Week 3 have been collected from at least 12 subjects for each dose and combination cohorts, PK sampling may be reduced for these visits.

15. Paired fresh biopsies must be provided pre- and post-dose at time points indicated. If it is not feasible to obtain a fresh biopsy, an archival sample must be provided. Fresh biopsies should be paired with plasma and whole blood samples for PK and circulating biomarkers collected as close as possible to biopsy (ideally within 1h). Subjects must have a platelet count of ≥75,000/mm3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy procedures and must have received at least 4 consecutive doses of GSK525762 prior to the collection of the tissue. If the on-therapy biopsy is not performed during the defined timeline due to lab abnormalities or subject status, it should be performed after subject recovery and the next visit as agreed upon with the medical monitor. Refer to the SRM for further details
18. CTC-ENU: Whole blood samples will be obtained for CTC enumeration at Screening (collected within 7 days prior to treatment), ~~Screening;~~ pre-dose on W1D1 of the combination treatment period, W5D1, W9D1 and every 8 weeks for the first 6 months and thereafter every 12 weeks; and EOT.
19. CTC-ARV: Whole blood samples will be obtained for measuring AR-Vs at pre-dose on W1D1~~, W5D1, and W9D1 of the combination treatment period; and EOT~~. Based on emerging data, GSK may decide to discontinue the collection of these samples.

Table 8 Dose Escalation Time and Events, Laboratory Assessments

		Week 1		Week 2		Week 3		Week 4	Week 5	Week 6	q2w	q4w	q4w	q12w	
	SCR	D1	D4	D1	D4	D1	D4	D1	D1	D1	W7 and 11	W9 to W49	W49 and thereafter	W49 and thereafter	EOT
Clinical chemistry	X	X	X	X		X		X	X	X[2]	X[2]	X	X[2]	X	X
Hematology	X	X	X	X	X	X	X	X	X	X[2]	X[2]	X	X[2]	X	X
Liver chemistry	X	X	X	X	X	X	X	X	X	X[2]	X[2]	X	X[2]	X	X
Coagulation	X	X	X	X		X		X	X	X[2]	X[2]	X	X[2]	X	X
Thyroid stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4))[3]	X								X			X		X	X

3. TSH testing is mandatory. T4 testing is only required if TSH is abnormal. T3 testing is required when clinically applicable (if both TSH and T4 are abnormal).

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	D 1	D 1	D 1	D 1	W9 to W49	W9 to W49	W49 and thereafter	
Safety											
12-lead ECGs ~~(Triplicate)~~[6]	X		X	X	X	X	X	X		X	X
Echocardiogram or MUGA[8]	X		~~X~~				X	Weeks 13, 25 and 37		X	X
Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)											
Tumor biopsy[13]	X				One sample, collected 3-6h post-GSK525762 dose, between W3D1 and W45D1						X[14]
Biomarker Assessments											
CTC – ARV[17]			X				~~X~~	~~Week 9 only~~			~~X~~

3. Screening echocardiogram or MUGA scans should be completed within 35 days prior to the first dose of study drugs. ~~Baseline imaging should be completed within 28 days prior to first dose of study drugs~~. All other assessments should be within 28~~14~~ 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.
7. Triplicate ECG~~s~~ 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.
14. "PK" = serial PK days. Sample collections should be obtained at the following timepoints: Pre-dose, 30m ± 5m, 1h ± 10m, 3h ± 30m, 6 to 12 hours and 24 h± 2h but prior to dosing. "O" = sample collections to be obtained pre-dose, 0.5-1h post-dose, and an optional sample 4-12h post-dose. "X" = sample collections to be obtained pre-dose as well as 0.5-1h post-dose (note that routine PK is no longer required once the subject has been on study for 26 weeks). PK samples will be split to obtain PK samples for abiraterone and enzalutamide. Abiraterone PK samples will be collected at all PK time points in Week 1 and Week 3 and only at pre-dose at remaining PK visits. Enzalutamide PK samples will be collected at pre-dose for all PK visits. Refer to the SRM for further details. For subjects in alternate dosing schedule, the Week 3 Day 1 extensive PK will need to occur between W2 Day 4 and W2 Day 7 prior to their scheduled dose interruption. For any PK timepoint, subjects should have received GS525762 for at least 7 days prior to their scheduled PK draws. This may require the subject to return earlier than any planned interruption of dosing. Once extensive PK sampling in Week 1 and Week 3 have been collected from at least 12 subjects for each dose and combination cohorts, PK sampling may be reduced for these visits.
15. Paired fresh biopsies must be provided pre- and post-dose at time points indicated. If it is not feasible to obtain a fresh biopsy, an archival sample must be provided. Fresh biopsies should be paired with plasma and whole blood samples for PK and circulating biomarkers collected as close as possible to biopsy (ideally within 1h). Subjects must have a platelet count of ≥75,000/mm3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy procedures and must have received at least 4 consecutive doses of GSK525762 prior to the collection of the tissue. If the on-therapy biopsy is not performed during the defined timeline due to

lab abnormalities or subject status, it should be performed after subject recovery and the next visit as agreed upon with the medical monitor. Refer to the SRM for further details

18. CTC-ENU: Whole blood samples will be obtained for CTC enumeration at Screening (collected within 7 days prior to treatment), ~~Screening,~~ pre-dose on W1D1 of the combination treatment period, W5D1, W9D1 and every 8 weeks for the first 6 months and thereafter every 12 weeks; and EOT.
19. CTC-ARV: Whole blood samples will be obtained for measuring AR-Vs at pre-dose on W1D1~~, W5D1, and W9D1 of the combination treatment period; and EOT~~. Based on emerging data, GSK may decide to discontinue the collection of these samples.

Table 10 Dose Expansion Time and Events, Laboratory Assessments

	SCR	Week 1 D1	Week 2 D1	Week 3 D1	Week 4 D1	Week 5 D1	Week 6 D1	q2w W7 and 11	q4w W9 to W49	q4w W49 and thereafter	q12w W49 and thereafter	EOT
Clinical chemistry	X	X	X	X	X	X	X[2]	X[2]	X	X[2]	X	X
Hematology	X	X	X	X	X	X	X[2]	X[2]	X	X[2]	X	X
Liver chemistry	X	X	X	X	X	X	X[2]	X[2]	X	X[2]	X	X
Coagulation	X	X	X	X	X	X	X[2]	X[2]	X	X[2]	X	X
Thyroid (Thyroid stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4))[3]	X					X			X		X	X

3. TSH testing is mandatory. T4 testing is only required if TSH is abnormal. T3 testing is required when clinically applicable (if both TSH and T4 are abnormal).

Section 7.2. – Screening and Critical Baseline Assessments

Rationale for Change:

Updated Screening window period.

Previous text:

All subjects must sign written Informed Consent prior to the commencement of any study specific screening procedures. Consent may be obtained up to 14 days prior to Cycle 1 Day 1. Subjects will have a screening period of up to 14 days prior to Cycle 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.

Revised text:

All subjects must sign written Informed Consent prior to the commencement of any study specific screening procedures. Consent may be obtained up to 28~~14~~ days prior to Week~~Cycle~~ 1 Day 1. Subjects will have a screening period of up to 28~~14~~ days prior to Week~~Cycle~~ 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.

Section 7.2.2. – Visit Windows

Rationale for Change:

Revisions to section wording to reflect changes to Screening period, assessments to be completed during Screening and clarification to PK language when alternate dose schedule may be utilized.

Previous text:

Screening (baseline to pre-dose): Screening echocardiogram or MUGA scan should be completed within 35 days and baseline imaging within 28 days prior to the first dose of study drugs. All other assessments should be completed within 14 days prior to first dose of study drugs. Clinical labs performed during screening within 72 hours of first dose do not need to be repeated on Day 1.

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. If a subject is not receiving GSK525762 on Week 3 Day 1 (either as a consequence of a planned drug holiday or due to toxicity), then serial PK collection should be rescheduled for a later time point when the subject is again being dosed steady state, 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.

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 ± 5 days.

Revised text:

Screening (baseline to pre-dose): Screening echocardiogram or MUGA scan should be completed within 35 days prior to first dose of study drugs.~~, and baseline imaging within 28 days prior to the first dose of study drugs.~~ All other assessments should be completed within 28~~14~~ 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 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 ~~(either~~ as a consequence of a planned drug holiday ~~or due to toxicity)~~, 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~~at steady state~~, 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.

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 ± 5 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.

Section 7.3.4.1. – Electrocardiograms

Rationale for Change:

Revisions to section wording to reflect updated recommendations from internal safety group after review of additional treatment data from subjects who have received GSK525762.

Previous text:

Triplicate 12-lead ECGs will be obtained, 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 >450 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.

Baseline results are defined by the nearest timepoint prior to first dose. For this trial the baseline QTcF value is determined by the mean of the triplicate W1D1 predose QTcF results. If these results are not available, then the mean QTcF of the screening triplicate ECG results should be used.

Revised text:

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 >4~~5~~80 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.

~~Baseline results are defined by the nearest timepoint prior to first dose. For this trial t~~The baseline QTcF value is determined by the mean of the triplicate Screening ~~W1D1 predose QTcF results. If these results are not available, then the mean QTcF of the screening triplicate~~ ECG results.~~should be used.~~

Section 7.3.5. – Clinical Safety Laboratory Assessments

Rationale for Change:

Clarifications to Table 11. Only relevant changes are reflected in the previous and revised text sections.

Previous text:

Table 11 Clinical Laboratory Tests

Clinical Chemistry	
Blood Urea Nitrogen	Albumin
Liver Function	
Bilirubin (Total and Direct)	
Cardiac Studies	
Troponin (I or T at local laboratory)	

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 10 and Table 12 for timing of required studies

Revised text:

Clinical Chemistry	
Blood Urea Nitrogen[a]	Albumin
Liver Function	
Bilirubin (Total and Direct)[b]	
Cardiac Studies	
Troponin (I or T at local laboratory, may be collected at central laboratory if local draw is not possible)	

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~~10~~ and Table 10~~12~~ for timing of required studies

Section 7.3.7. – Pregnancy

Rationale for Change:

Revision to provide consistency with revised template language.

Previous text:

Details of all pregnancies in female partners of male subjects will be collected after the start of dosing and until at least 4 months post-last dose. …

… Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

Revised text:

Details of all pregnancies in female partners of male subjects will be collected after the start of dosing and until at least 16 weeks~~4 months~~ post-last dose. …

… While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

~~Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.~~

Section 7.5.1. – Tumor Biopsy Collection/Surgical Procedures

Rationale for Change:

Revisions to update Screening period and add language to flexibility of timing of on therapy sample collection.

Previous text:

In the dose escalation and expansion cohort(s), paired fresh biopsies must be provided pre- (within 14 days of the first dose) and on-treatment at the time points indicated from all the subjects. Any fresh on-treatment biopsy should be accompanied by a whole blood sample collected as close as possible to the time of biopsy (preferably within 1h). Subjects providing an on-treatment fresh tumor biopsy must have received at least 4 consecutive days of GSK525762 prior to the collection of the sample. Further details regarding sample type and processing will be provided in the SRM. If a potential subject does not have disease amenable to biopsy, participation may occur only upon discussion with and approval of the medical monitor; in this situation, an archival tumor sample retrieved after completion of most recent ADT will be required.

Subjects must have a platelet count of ≥75,000/mm3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy or any other planned surgical procedure. Further details regarding sample type and processing will be provided in the SRM.

Revised text:

In the dose escalation and expansion cohort(s), paired fresh biopsies must be provided pre- (within 28~~14~~ days of the first dose) and on-treatment at the time points indicated from all the subjects. Any fresh on-treatment biopsy should be accompanied by a whole blood sample collected as close as possible to the time of biopsy (preferably within 1h). Subjects providing an on-treatment fresh tumor biopsy must have received at least 4 consecutive days of GSK525762 prior to the collection of the sample. Further details regarding sample type and processing will be provided in the SRM. If a potential subject does not have disease amenable to biopsy, participation may occur only upon discussion with and approval of the medical monitor; in this situation, an archival tumor sample retrieved after completion of most recent ADT will be required.

Subjects must have a platelet count of ≥75,000/mm3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy or any other planned surgical procedure. If the on therapy biopsy is not performed during the defined timeline due to lab abnormalities or subject status, it should be performed after subject recovery and the next visit as agreed upon with the medical monitor. Further details regarding sample type and processing will be provided in the SRM.

Section 7.6.1. – Disease Progression Endpoint

Rationale for Change:

Revisions to definition of PSA progression.

Previous text:

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

- PSA progression according to the PCWG3 criteria (Section 7.6.2)
- 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)

Revised text:

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

- ~~PSA progression according to the PCWG3 criteria (Section 7.6.2)~~
- 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

Section 7.7.3. – Circulating Tumor Cells

Rationale for Change:

Revisions to reflect changes in collection time points for CTC-ARV sampling and clarification to CTC enumeration language.

Previous text:

Blood samples will be collected and analyzed to enumerate CTCs in circulation at the time points indicated in the Time and Events Tables (Section 7.1). The CTCs may also be utilized for additional analysis like alterations in AR genes and may include additional genes implicated in the prostate cancer or related to AR signaling pathway. If baselines CTCs are not observed in a subject, GSK may ask to terminate the further sampling for CTC enumeration in those subjects.

Additional blood samples will be collected at the time points indicated in the Time and Events Tables (Section 7.1) to isolate CTCs. The isolated CTCs will be analyzed for AR variants or other protein markers and potential genomic alterations (e.g. AR amplifications, phosphatase and tensin homolog (PTEN) allele loss etc.). Based on emerging data, GSK may decide to discontinue the collection of these samples.

Revised text:

Blood samples will be collected and analyzed to enumerate CTCs in circulation at the time points indicated in the Time and Events Tables (Section 7.1). The CTCs may also be utilized for additional analysis like alterations in AR genes and may include additional genes implicated in the prostate cancer or related to AR signaling pathway. ~~If baselines CTCs are not observed in a subject, GSK may ask to terminate the further sampling for CTC enumeration in those subjects.~~

~~Additional blood samples will be collected at the time points indicated in the Time and Events Tables (Section 7.1) to isolate CTCs. The isolated CTCs will be analyzed for AR variants or other protein markers and potential genomic alterations (e.g. AR amplifications, phosphatase and tensin homolog (PTEN) allele loss etc.). Based on emerging data, GSK may decide to discontinue the collection of these samples.~~

Section 9.1 – Hypotheses

Rationale for Change:

Revisions to correct language in error from previous version and to clarify conduct of analyses. Update language based provided by Berry Consulting. language reflect changes in collection time points for CTC-ARV sampling and clarification to CTC enumeration language.

Previous text:

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 GSK2879552 plus azacitidine in subjects with advanced cancer.

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 response rate and safety.

The 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 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 the largest utility relative to other doses may be picked as the RP2D. Further details of the calculation of utility function will be provided in RAP….

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 PSA results or have progressed or died or permanently withdraw from the study.

For the separate interim looks in each combination in expansion cohort, the enrolment for that cohort may be stopped due to futility if the predictive probability that the expected utility (dU) >CSMU (20) is small (e.g., less than a 4% chance for the expected utility to be larger than the CSMU). At the final analysis for each dose combination, the dose will be claimed positive if the posterior probability that the expected utility (dU) >CSMU (20) is at least 20%.

No formal hypotheses are set up to compare the activity between the two dose levels. The difference of response rate and R 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 the largest utility relative to other doses 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 totally of data.

Revised text:

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 ~~GSK2879552~~ GSK525762 plus abiraterone or enzalutamide ~~azacitidine~~ in subjects with CRPC~~advanced cancer~~.

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 ~~response rate~~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 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 ~~the largest utility relative to other doses~~ 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 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~~withdraw~~ 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 ~~predictive~~posterior probability that the ~~expected~~ utility (dU) >CSMU (~~20~~25) is small (e.g., less than a 4% chance for the ~~expected~~ 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 ~~expected~~ utility (dU) >CSMU (25~~20~~) 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 ~~and R~~ 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 ~~the largest utility relative to other doses~~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 ~~totally~~totality of data.

Section 9.3.1. – Analysis Populations

Rationale for Change:

Clarifications of the analysis populations.

Previous text:

The **All Treated Safety Population** is defined as all subjects who receive at least one dose of GSK525762 or abiraterone or enzalutamide. Safety and anti-cancer activity will be evaluated based on this analysis population.

The **All Clinical Activity Treated Population** is defined as all subjects who receive at least one dose of GSK525762 plus abiraterone/enzalutamide. Safety and anti-cancer activity will be evaluated based on this analysis population.

All Evaluable Subjects will be defined as the study population used for decision-making at the interim futility analysis. Subjects who have at least two post-baseline radiological disease assessments or have had Week 12 visit PSA test results or have progressed or died or permanently withdrew from the study will be included in this population.

Revised text:

The **All Treated ~~Safety~~ Population** is defined as all subjects who receive at least one dose of GSK525762 or abiraterone or enzalutamide. Safety and anti-cancer activity will be evaluated based on this analysis population.

The **Modified All ~~Clinical Activity~~ Treated Population** is defined as all subjects who receive at least one dose of GSK525762 plus abiraterone/enzalutamide. Safety and anti-cancer activity will be evaluated based on this analysis population if different from the All Treated Population.

All Evaluable Subjects will be defined as the study population used for decision-making at the interim futility analysis. Subjects who have ~~at least two post-baseline radiological disease assessments or have~~ had Week 12 or later visit ~~PSA test~~disease assessment results or have progressed according to the guidelines described in Section 7.6.1 or died or permanently withdrew from the study treatment will be included in this population.

Section 9.3.2.2.1. – Efficacy Anayses

Rationale for Change:

Revision to language for consistency with remainder of protocol and clarifications on decision criteria for Interim Analyses.

Previous text:

Interim analysis will be conducted for each DL separately. Interim data will be evaluated to monitor efficacy and safety, and a planned interim analysis will be performed when 10 evaluable subjects are available at any DL. Enrollment may be stopped early in any of the expansion cohorts for toxicity or lack of efficacy, should various criteria occur based on accrued data. The decision criteria for early stop for futility based on Bayesian probability are described in Section 9.1.2.

Revised text:

Interim analysis will be conducted for each DL separately. Interim data will be evaluated to monitor efficacy and safety, and a planned interim analysis ~~will~~ may be performed when at least 10 evaluable subjects are available at any DL. Enrollment may be stopped early in any of the expansion cohorts for toxicity or lack of efficacy, should various criteria occur based on accrued data. The decision ~~criteria for early~~to stop enrolment within a cohort for futility ~~based on Bayesian probability are described in Section 9.1.2.~~will be based on the totality of the data including safety/tolerability and evaluation of primary and secondary efficacy endpoints.

Section 9.4.1.2. – Adverse Events

Rationale for Change:

Clarification to language.

Previous text:

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

Revised text:

… Dose-limiting toxicities (DLTs) will be listed for ~~Phase I~~dose escalation subjects and summarized by dose cohort. ~~according to International Data Standards Library (IDSL) standards~~….

Section 9.4.4. – Efficacy Analyses

Rationale for Change:

Addition of Secondary Efficacy Endpoint and clarifications to other definitions. Only definitions updated are presented.

Previous text:

The following secondary responses will also be considered for drawing conclusions on the clinical activity of the combination(s):

Duration of PSA response

Duration of PSA response is calculated from the time the PSA value first declines by at least 50% of the Cycle 1 Day 1 (baseline) value (must be confirmed by a second value) until the time there is an increase of 25% of PSA nadir, provided the absolute increase is at least 2 ng/mL. The increase must be confirmed by a second consecutive measurement that is at least 25% above the nadir. If the PSA never shows a 25% increase over the nadir value, then the patient will be assessed at the last PSA measurement. Duration of

PSA response will be summarised by the median and presented along its 95% confidence interval.

ORR

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

CTC Response

CTC response rate is defined as the proportion of subjects with a CTC conversion to <5/7.5 mL blood at nadir (confirmed by a second consecutive value obtained four or more weeks later) will be presented along an exact two-sided 95% confidence interval. Waterfall plots of maximum CTC falls will also be presented that show the percentage change in CTC counts from baseline. The CTC response need to be confirmed by a second consecutive value obtained four or more weeks later.

Time to disease progression is according to PCWG3 criteria (either by PCWG3-modified RECIST 1.1, PSA progression, and/or progression in bone).

For the analysis of **overall survival (OS)**, the last date of known contact will be used for those subjects who have not died at the time of analysis; such subjects will be considered censored. Further details on rules for censoring will be provided in the RAP. If data warrant, OS will be summarized by cohort and dose level specified in Phase I-using Kaplan-Meier quantile estimates along with 2-sided 95% CIs at the time of end of Phase 1 interim analysis.

Revised text:

The following secondary responses will also be considered for drawing conclusions on the clinical activity of the combination(s):

Disease Control Rate at 24 weeks

Disease control rate (DCR) is defined as the percentage of subjects with SD, PR or CR at ≥ 24 weeks. Subjects with unknown or missing response will be treated as non-responders (i.e. these subjects will be included in the denominator when calculating the percentage).

Duration of PSA response

Duration of PSA response is calculated from the time the PSA value first declines by at least 50% of the Week~~Cycle~~ 1 Day 1 (baseline) value (must be confirmed by a second value) until the time there is an increase of 25% of PSA nadir, provided the absolute increase is at least 2 ng/mL. The increase must be confirmed by a second consecutive measurement that is at least 25% above the nadir. If the PSA never shows a 25% increase

over the nadir value, then the patient will be ~~assessed~~censored at the last PSA measurement. Duration of PSA response will be summarised by the median and presented along its 95% confidence interval.

ORR

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

CTC Response

CTC response rate is defined as the proportion of subjects with a CTC conversion to <5/7.5 mL blood at nadir (confirmed by a second consecutive value obtained four or more weeks later) will be presented along an exact two-sided 95% confidence interval. Subjects with CTC<5/7.5 mL at baseline will be excluded from this analysis. Waterfall plots of maximum CTC falls will also be presented that show the percentage change in CTC counts from baseline. The CTC response need to be confirmed by a second consecutive value obtained four or more weeks later.

Time to disease progression

Time to disease progression is defined as time from first dose date of study treatment to disease progression ~~according to~~ defined as one or more of the following criteria:

- Radiographic progression 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.

~~PCWG3 criteria (either by PCWG3-modified RECIST 1.1, PSA progression, and/or progression in bone).~~ Subjects without disease progression at the time of analysis will be censored at the earlier date of last PSA assessment and last radiological assessment.

For the analysis of **overall survival (OS)**, the last date of known contact will be used for those subjects who have not died at the time of analysis; such subjects will be considered censored. Further details on rules for censoring will be provided in the RAP. If data warrant, OS will be summarized by arm~~cohort~~ and dose level ~~specified in Phase I~~ using Kaplan-Meier quantile estimates along with 2-sided 95% CIs ~~at the time of end of Phase 1 interim analysis~~.

Appendix 2: – Management of Suspected Toxicity

Rationale for Change:

Removal and revision of QTc language per updated guidance by internal safety review panel.

Previous text:

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
QTcF	If >30msec and < 60 msec change from baseline AND manual QTcF <500 (average of three ECGs over at least 15 minutes)	Continue current dose of GSK525762 • Evaluation by cardiologist • Supplement electrolytes, particularly potassium and magnesium, to recommended levels: a. Maintain serum potassium > 4mol/L b. Maintain serum magnesium levels >0.85 mmol/L • Discontinue any concomitant medications with potential for QTcF prolongation. • Consider 24 hour or longer telemetry monitoring if clinically indicated.

	If ≥ 60 msec change from baseline occurs OR QTcF ≥500 (average of three ECGs over at least 15 minutes)	Discontinue GSK525762 and notify the Medical Monitor. • Supplement electrolytes to recommended levels: a. Maintain serum potassium > 4mol/L b. Maintain serum magnesium levels >0.85 mmol/L • Rule out other potential etiologies for prolonged QTcF such as cardiac ischemia • Discontinue any concomitant medications with potential for QTcF prolongation. • Consider telemetry monitoring if clinically indicated. This subject may consider restarting study treatment at one dose level reduced if all of the following criteria for QTcF re-challenge are met. In France, if stopping criteria is met, subjects will not be allowed to restart or be rechallenged. If approval for re-challenge is granted, the subject must be re-consented (with a separate informed consent specific to QTc prolongation) (1) QTcF reduced to <4~~8~~50 msec, (2) Potassium and magnesium levels are within institutional normal range, (3) A favorable risk/benefit profile (in the medical judgement of the Investigator and the Medical Monitor), (4) Approval within GSK medical governance: a. agreement with SERM MD and PPL, b. review with Chair or co-Chair of the GSK QT panel, c. SERM VP and Clinical VP approval d. Head Unit Physician approval (5) Institutional IRB (or equivalent) approval, if required by IRB (or equivalent), and (6) The subject is re-consented regarding the possible increased risk of QTc prolongation. Discontinuation procedures: If the subject is withdrawn due to QTcF event, the subject should complete the following activities post-dose: (1) Evaluation by cardiologist. (2) Weekly assessments for QTcF until ≤30 msec change from baseline reached, and then next assessment at 4 weeks post-dose. (3) If QTcF results have not resolved to baseline by 4 weeks post-dose, then continue every 4-5 weeks until resolution

Revised text:

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
QTcF	~~If >30msec and < 60 msec change from baseline AND manual QTcF <500 (average of three ECGs over at least 15 minutes)~~	~~Continue current dose of GSK525762~~ • ~~Evaluation by cardiologist~~ • ~~Supplement electrolytes, particularly potassium and magnesium, to recommended levels:~~ ~~a. Maintain serum potassium > 4mol/L~~ ~~b. Maintain serum magnesium levels >0.85 mmol/L~~ • ~~Discontinue any concomitant medications with potential for QTcF prolongation.~~ • ~~Consider 24 hour or longer telemetry monitoring if clinically indicated.~~

	If ≥ 60 msec change from baseline occurs AND~~OR~~ QTcF ≥500 msec OR QTcF≥530 msec AND <60 msec change from baseline ~~occurs~~ (average of three ECGs over at least 15 minutes)	Discontinue GSK525762 and notify the Medical Monitor. • Evaluation by cardiologist • Supplement electrolytes to recommended levels: a. Maintain serum potassium > 4mol/L b. Maintain serum magnesium levels >0.85 mmol/L • Rule out other potential etiologies for prolonged QTcF such as cardiac ischemia • Discontinue any concomitant medications with potential for QTcF prolongation. • ~~Consider~~ 24-hour telemetry monitoring if clinically indicated. This subject may consider restarting study treatment at one dose level reduced if all of the following criteria for QTcF re-challenge are met. In France, if stopping criteria is met, subjects will not be allowed to restart or be rechallenged. If approval for re-challenge is granted, the subject must be re-consented (with a separate informed consent specific to QTc prolongation) (1) QTcF reduced to <485~~5~~0 msec, (2) Potassium and magnesium levels are within institutional normal range, (3) A favorable risk/benefit profile (in the medical judgement of the Investigator and the Medical Monitor), (4) Approval within GSK medical governance: a. agreement with SERM MD and PPL, b. review with Chair or co-Chair of the GSK QT panel, c. SERM VP and Clinical VP approval d. Head Unit Physician approval (5) Institutional IRB (or equivalent) approval, if required by IRB (or equivalent), and (6) The subject is re-consented regarding the possible increased risk of QTc prolongation. Discontinuation procedures: If the subject is withdrawn due to QTcF event, the subject should complete the following activities post-dose: (1) Evaluation by cardiologist. (2) Weekly assessments for QTcF until ≤30 msec change from baseline reached, and then next assessment at 4 weeks post-dose. (3) If QTcF results have not resolved to baseline by 4 weeks post-dose, then continue every 4-5 weeks until resolution

Appendix 8: – Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

Rationale for Change:

Removal of language regarding protocol specific SAEs to clarify all SAEs are followed until resolution.

Previous text:

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
h. Protocol-specific SAEs (events of special interest): LVEF decreases (Section 5.4.3) meeting stopping criteria Liver chemistry abnormalities meeting stopping criteria (Section 5.4.1) QTcF prolongation meeting stopping criteria (Section 5.4.2) New primary cancers

Revised text:

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
~~**i. Protocol-specific SAEs (events of special interest):**~~ ~~LVEF decreases (Section 5.4.3) meeting stopping criteria~~ ~~Liver chemistry abnormalities meeting stopping criteria (Section 5.4.1)~~ ~~QTcF prolongation meeting stopping criteria (Section 5.4.2)~~ ~~New primary cancers~~

Appendix 12: ~~Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information~~ Contraception Guidance and Collection of Pregnancy Information

Rationale for Change:

Revision to language based on update of GSK template language.

Previous text:

12.12.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

The list does not apply to male subjects with partners of FRP who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation,

symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Contraceptive requirements for male subjects with female partners of reproductive potential (when applicable)

Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until 4 month after the last dose of study medication.

1. Sterilization with documentation of azoospermia. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview.
2. Male condom plus partner use of intrauterine device or intrauterine system.

Note: Hormonal methods of contraception for female partners of FRP are not permitted since the efficacy of these methods in combination with GSK525762 has not been assessed. Hormone-releasing IUDs are a permitted form of contraception. LHRH-acting agents alone are not considered an adequate form of contraception.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.12.2. Collection of Pregnancy Information

- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomized to receive study medication.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 weeks of learning of the partner's pregnancy
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Revised text:

~~**12.12.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)**~~

~~The list does not apply to male subjects with partners of FRP who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.~~

~~Contraceptive requirements for male subjects with female partners of reproductive potential (when applicable)~~

~~Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until 4 month after the last dose of study medication.~~

1. ~~Sterilization with documentation of azoospermia. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview.~~
2. ~~Male condom plus partner use of intrauterine device or intrauterine system.~~

~~Note: Hormonal methods of contraception for female partners of FRP are not permitted since the efficacy of these methods in combination with GSK525762 has not been assessed. Hormone-releasing IUDs are a permitted form of contraception. LHRH-acting agents alone are not considered an adequate form of contraception.~~

~~These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.~~

12.12.1. Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
• **Highly Effective Methods[b] That Have Low User Dependency**
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner   • *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
• **Highly Effective Methods[b] That Are User Dependent**

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  • oral
  • injectable

• Sexual abstinence   • *Note: Sexual abstinence is considered a highly effective method only if defined as*

refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

12.12.2. Collection of Pregnancy Information

- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomized to receive study medication.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours ~~weeks~~ of learning of the partner's pregnancy
- Female p~~P~~artner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Other changes to provide additional clarifications or to correct inadvertent errors in previous versions of the protocol:

Title Page:

Updated author list to include new authors: PPD, PPD and remove PPD and PPD

Sponsor Signatory:

Replacement of Li Yan with Michael Streit as signatory. Revision of Table of Contents to reflect changes protocol addressed earlier in this Appendix.

Sponsor contact information:

Addition of PPD as primary medical monitor and movement of PPD to secondary medical monitor; removal of PPD.

References:

Updated reference of the GSK525762 Investigator's Brochure to current version.

Reference to Lee, 2008 removed.

List of Abbreviations:

Addition of new abbreviations to table: DCR – Disease Control Rate

Protocol changes for Amendment 4 (06-May-2020) from Amendment 3 (12-Jul-2018)

Protocol Amendment 04 applies to all global site(s) participating in the conduct of the study

Amendment 04 summary:

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. The study will conclude when the last subject has completed/discontinued study treatment and completed the end of treatment visit.

Changes to the protocol include:

- Enrolment into the study is now closed
- Removes the requirement for specific protocol assessments and survival follow-up (Section 7.1 – Time and Events Tables)
- Update to the GSK authors, GSK signatory and GSK medical monitor

List of Specific Changes

Title Page

Rationale for Change: Update to protocol author list

Revised text:

Author (s): PPD
PPD

SPONSOR SIGNATORY

Rationale for Change: Update to sponsor signatory

Revised text:

Hesham A. Abdullah, MD, MSc, RAC
~~Michael Streit, MD~~
SVP, Head of Clinical Development, Oncology~~Clinical Development Lead, Oncology~~

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Rationale for Change: Update to Medical Monitor information

Revised text:

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Site Address
Primary Medical Monitor	PPD MD	PPD	PPD	GSK R&D, Gunnels Wood, Stevenage, Herts, SG1 2NY PPD PPD ~~GlaxoSmithKline~~ ~~1250 South Collegeville Road, UP4410~~ ~~Collegeville, PA 19426, USA~~ PPD

Section 1. PROTOCOL SYNOPSIS FOR STUDY 204697

Rationale for Change: 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. Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

Revised text:

Analysis

Last Paragraph

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. The study will conclude when the last subject has completed/discontinued study treatment and completed the end of treatment visit.

Section 4.3. Decision to Proceed to Expansion phase

Rationale for Change: 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. Specific

assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

Revised text:

First Paragraph

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.

Section 5.5. Subject and Study Completion

Rationale for Change: 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. Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

Revised text:

Last Paragraph

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.

Section 7.1. Time and Events Table

Rationale for Change: 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. Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

Revised text:

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 there after	
Safety														

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 there after	
PRO-CTCAE[9]	X		~~X~~		~~X~~		~~X~~		~~X~~	~~X~~	~~X~~		~~X~~	~~X~~
Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)														
PK blood samples[12]			~~PK~~				~~PK~~			~~O~~		~~X~~		
Tumor biopsy[13]	X						~~One sample, collected 3-6h post-GSK525762 dose, between W3D1 and W5D1~~							~~X~~[14]
Whole blood for exploratory analyses[14]	X		~~X~~				~~X~~[15]					~~Q8wks up to six months, then Q12 wks~~	~~X~~	~~X~~
PGx blood sample[15]			X											
Biomarker Assessments														
CTC-ENU[16]	X		~~X~~							~~X~~		~~Q8wks up to six months, then Q12 wks~~	~~X~~	~~X~~
CTC – ARV[17]			~~X~~											
Efficacy														
Computerized Tomography (CT) chest/abdomen/pelvis[18]	X											~~Q8wks up to six months, then Q12 wks~~	~~X~~	~~X~~
MRI Brain[19]	X													

Procedure	SCR	Lead-In Dosing (if required)	Week 1		Week 2		Week 3		Week 4	Week 5	q4w	q8w	q12w	EOT[1, 22]
			D 1	D 4	D 1	D 4	D 1	D 4	D 1	D 1	W9 to W49	W9 to W49	W49 and there after	
Bone Scan[20]	X											~~Q8wks up to six months, then Q12 wks~~	~~X~~	
EORTC-QLQ-C30, EORTC-QLQ-PR25 & BPI-SF[21]	X		~~X~~		~~X~~		~~X~~		~~X~~	~~X~~	~~X~~		~~X~~	~~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.** ~~Following this visit, subjects will be contacted approximately every 3 months (± 14 days) to collect: survival status as of last date of contact and initiation of new anti-cancer therapy. Contact may be completed via a clinic visit, a telephone contact or an email~~.

9. **With the implementation of amendment 04, the PRO-CTCAE will no longer be collected.**~~Patient Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Item Library (Version 1.0)~~

12. **With the implementation of amendment 04, PK samples will no longer be collected.** ~~"PK" = serial PK days. Sample collections should be obtained at the following timepoints: Pre-dose, 30m ± 5m, 1h ± 10m, 3h ± 30m, 6 to 12 hours and 24 h± 2h but prior to dosing. "O" = sample collections to be obtained pre-dose, 0.5-1h post-dose, and an optional sample 4-12h post-dose. "X" = sample collections to be obtained pre-dose as well as 0.5-1h post-dose (note that routine PK is no longer required once the subject has been on study for 26 weeks). PK samples will be split to obtain PK samples for abiraterone and enzalutamide. Abiraterone PK samples will be collected at all PK time points in Week 1 and Week 3 and only at pre-dose at remaining PK visits. Enzalutamide PK samples will be collected at pre-dose for all PK visits. Refer to the SRM for further details. For subjects in alternate dosing schedule, the Week 3 Day 1 extensive PK will need to occur between W2 Day 4 and W2 Day 7 prior to their scheduled dose interruption. For any PK timepoint, subjects should have received GS525762 for at least 7 days prior to their scheduled PK draws. This may require the subject to return earlier than any planned interruption of dosing. Once extensive PK sampling in Week 1 and Week 3 have been collected from at least 12 subjects for each dose and combination cohorts, PK sampling may be reduced for these visits.~~

13. **With the implementation of amendment 04, on treatment and EOT tumor biopsies will no longer be collected.**~~Paired fresh biopsies must be provided pre- and post-dose at time points indicated. If it is not feasible to obtain a fresh biopsy, an archival sample must be provided. Fresh biopsies should be paired with plasma and whole blood samples for PK and circulating biomarkers collected as close as possible to biopsy (ideally within 1h). Subjects must have a platelet count of ≥75,000/mm3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy procedures and must have received at least 4 consecutive doses of GSK525762 prior to the collection of the tissue. If the on-therapy biopsy is not performed during the defined timeline due to lab abnormalities or subject status, it should be performed after subject recovery and the next visit as agreed upon with the medical monitor. Refer to the SRM for further details.~~

14. **With the implementation of amendment 04, whole blood for exploratory analyses will no longer be collected.**~~A tumor biopsy at the end of treatment is optional.~~

15. **With the implementation of amendment 04, if a PGx sample has not yet been collected, collection will no longer be required** ~~Whole blood for exploratory analysis at this time point should be collected as close to tumor biopsy collection.~~
16. **With the implementation of amendment 04, CTC-ENU whole blood samples will no longer be collected.** CTC-ENU: Whole blood samples will be obtained for CTC enumeration at Screening (collected within 7 days prior to treatment), pre-dose on W1D1 of the combination treatment period, W5D1, W9D1 and every 8 weeks for the first 6 months and thereafter every 12 weeks; and EOT.
17. **With the implementation of amendment 04, CTC-ARV whole blood samples will no longer be collected.** ~~CTC-ARV: Whole blood samples will be obtained for measuring AR-Vs at pre-dose on W1D1.Based on emerging data, GSK may decide to discontinue the collection of these samples.~~
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.** ~~CT should be performed with oral and intravenous (IV) contrast. CT required at screening. Any potential CR or PR should be confirmed as described in Appendix 5. Assessments will occur every 8 weeks (±7 days) for the first 6 months and thereafter every 12 weeks (±7 days) in the Treatment Continuation Period, or as clinically indicated, and at the time of disease progression. EOT disease assessment is not required if reason for discontinuing therapy was progressive disease and prior radiographic assessment was within 14 days of EOT visit. Subjects with contraindication to contrast-enhanced CT may have other imaging performed as described in Section 7.2.1.~~
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.** ~~Magnetic resonance imaging (MRI) of the brain required at screening and then as clinically indicated thereafter.~~
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.** ~~Bone Scan: A bone scan is required for all subjects at Screening. For subjects without bone disease at baseline, subsequent bone scans should be performed as clinically indicated. Subjects with bone metastases at baseline should have a bone scan performed at Week 9, then every 8 weeks (±7 days) for the first 6 months and thereafter every 12 weeks (±7 days) in the Treatment Continuation Period, or as clinically indicated, and at the time of disease progression. If a subject discontinues treatment for reasons other than disease progression, bone scans should continue every 3 months until disease progression, initiation of new anti-cancer treatment, subject withdrawal of consent, or death.~~
21. **With the implementation of amendment 04, quality of life questionnaires will no longer be collected.** ~~European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core-30, EORTC-QLQ-PR25, for evaluating prostate cancer, and Brief Pain Inventory- Short Form (BPI-SF).~~

Table 8 Dose Escalation Time and Events, Laboratory Assessments

		Week 1		Week 2		Week 3		Week 4	Week 5	Week 6	q2w	q4w	q4w	q12w	
	SCR	D1	D4	D1	D4	D1	D4	D1	D1	D1	W7 and 11	W9 to W49	W49 and thereafter	W49 and thereafter	EOT
PSA [2]	X	~~X~~							~~X~~			~~X~~	~~X~~[2]	~~X~~	~~X~~

2. **With the implementation of amendment 04, samples for PSA will no longer be collected. Disease assessment should be managed according to local standard of care.** ~~Local labs can be used to collect this information.~~

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	D 1	D 1	D 1	D 1	W9 to W49	W9 to W49	W49 and thereafter	
Safety											
PRO-CTCAE[9]	X		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~		~~X~~	~~X~~
Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)											
PK blood samples[12]			~~PK~~		~~PK~~		~~O~~		~~X~~		
Tumor biopsy[13]	X				~~One sample, collected 3-6h post-GSK525762 dose, between W3D1 and W5D1~~						~~X~~[14]
Whole blood for exploratory analyses[14]	X		~~X~~		~~X~~[15]				~~Q8wks up to six months, then Q12wks~~	~~X~~	~~X~~
PGx blood sample[15]			X								
Biomarker Assessments											
CTC-ENU[16]	X		~~X~~				~~X~~		~~Q8wks up to six months, then Q12wks~~	~~X~~	~~X~~
CTC – ARV[17]			~~X~~								
Efficacy											
CT chest/abdomen/pelvis[18]	X								~~Q8wks up to six months, then Q12wks~~	~~X~~	~~X~~
MRI Brain[19]	X										

Procedure	SCR	Lead-In Dosing (if required)	Week 1	Week 2	Week 3	Week 4	Week 5	q4w	q8w	q12w	EOT[1, 22]
			D1	D 1	D 1	D 1	D 1	W9 to W49	W9 to W49	W49 and thereafter	
Bone Scan[20]	X								~~Q8wks up to six months, then Q12wks~~	~~X~~	
EORTC-QLQ-C30, EORTC-QLQ-PR25 & BPI[21]	X		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~		~~X~~	~~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.** ~~Following this visit, subjects will be contacted approximately every 3 months (± 14 days) to collect: survival status as of last date of contact and initiation of new anti-cancer therapy. Contact may be completed via a clinic visit, a telephone contact or an email.~~

9. **With the implementation of amendment 04, the PRO-CTCAE will no longer be collected.**~~Patient Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Item Library (Version 1.0)~~

12. **With the implementation of amendment 04, PK sample will no longer be collected.**~~"PK" = serial PK days. Sample collections should be obtained at the following timepoints: Pre-dose, 30m ± 5m, 1h ± 10m, 3h ± 30m, 6 to 12 hours and 24 h± 2h but prior to dosing. "O" = sample collections to be obtained pre-dose, 0.5-1h post-dose, and an optional sample 4-12h post-dose. "X" = sample collections to be obtained pre-dose as well as 0.5-1h post-dose (note that routine PK is no longer required once the subject has been on study for 26 weeks). PK samples will be split to obtain a PK sample for all time points for Week 1 and Week 3 and only pre-dose for other visits for abiraterone and only for the pre-dose sample for enzalutamide and its active major metabolite analysis. Refer to the SRM for further details. For subjects in alternate dosing schedule, the Week 3 Day 1 extensive PK will need to occur between W2 Day 4 and W2 Day 7 prior to their scheduled dose interruption. For any PK timepoint, subjects should have received GS525762 for at least 7 days prior to their scheduled PK draws. This may require the subject to return earlier than any planned interruption of dosing. Once extensive PK sampling in Week 1 and Week 3 have been collected from at least 12 subjects for each dose and combination cohorts, PK sampling may be reduced for these visits.~~

13. **With the implementation of amendment 04, on treatment and EOT tumor biopsies will no longer be collected.**~~Paired fresh biopsies must be provided pre- and post-dose at time points indicated. If it is not feasible to obtain a fresh biopsy, an archival sample must be provided. Fresh biopsies should be paired with plasma and whole blood samples for PK and circulating biomarkers collected as close as possible to biopsy (ideally within 1h). Subjects must have a platelet count of ≥75,000/mm3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy procedures and must have received at least 4 consecutive doses of GSK525762 prior to the collection of the tissue. If the on-therapy biopsy is not performed during the defined timeline due to lab abnormalities or subject status, it should be performed after subject recovery and the next visit as agreed upon with the medical monitor. Refer to the SRM for further details.~~

~~14. A tumor biopsy at the end of treatment is optional.~~

1415. **With the implementation of amendment 04, whole blood for exploratory analyses will no longer be collected.**~~Whole blood for exploratory analysis at this time point should be collected as close to tumor biopsy collection.~~

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.** ~~CTC-ENU: Whole blood samples will be obtained for CTC enumeration at Screening (collected within 7 days prior to start of treatment), pre-dose on W1D1of the combination treatment period, W5D1, W9D1 and every 8 weeks for the first 6 months and thereafter every 12 weeks; and EOT.~~
17. **With the implementation of amendment 04, CTC-ARV whole blood samples will no longer be collected.** ~~CTC-ARV: Whole blood samples will be obtained for measuring AR-Vs at pre-dose on W1D1. Based on emerging data, GSK may decide to discontinue the collection of these samples.~~
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.** ~~CT should be performed with oral and intravenous (IV) contrast. CT required at screening. Any potential CR or PR should be confirmed as described in Appendix 5. Assessments will occur every 8 weeks (±7 days) for the first 6 months and thereafter every 12 weeks (±7 days) in the Treatment Continuation Period, or as clinically indicated, and at the time of disease progression. EOT disease assessment is not required if reason for discontinuing therapy was progressive disease and prior radiographic assessment was within 14 days of EOT visit. Subjects with contraindication to contrast-enhanced computed tomography (CT) may have other imaging performed as described in Section 7.2.1.~~
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.** ~~Magnetic resonance imaging (MRI) of the brain required at screening and then as clinically indicated thereafter.~~
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.** ~~Bone Scan: A bone scan is required for all subjects at Screening. For subjects without bone disease at baseline, subsequent bone scans should be performed as clinically indicated. Subjects with bone metastases at baseline should have a bone scan performed at Week 9, then every 8 weeks (±7 days) for the first 6 months and thereafter every 12 weeks (±7 days) in the Treatment Continuation Period, or as clinically indicated, and at the time of disease progression. If a subject discontinues treatment for reasons other than disease progression, bone scans should continue every 3 months until disease progression, initiation of new anti-cancer treatment, subject withdrawal of consent, or death.~~
21. **With the implementation of amendment 04, quality of life questionnaires will no longer be collected.** ~~European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core-30, EORTC-QLQ-PR25, for evaluating prostate cancer, and Brief Pain Inventory-Short Form (BPI-SF).~~

Table 10 Dose Expansion Time and Events, Laboratory Assessments

	SCR	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	q2w	q4w	q4w	q12w	EOT
		D1	D1	D1	D1	D1	D1	W7 and 11	W9 to W49	W49 and thereafter	W49 and thereafter	
PSA[2]	X	~~X~~				~~X~~			~~X~~	~~X~~[2]	~~X~~	~~X~~

1. **With the implementation of amendment 04, samples for PSA will no longer be collected. Disease assessment should be managed according to local standard of care** ~~Local labs can be used to collect this information.~~

Section 7.2.2. Visit Windows

Rationale for Change: 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. Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

Revised text:

First Paragraph

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.

Paragraph 8, First Sentence

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~~5~~ days.

Section 7.3.4.1. Electrocardiograms

Rationale for Change: Specific assessments, for purposes of the study, are being removed. Transfer of data to a central reader, for purposes of the study, is no longer required.

Revised text:

Last Paragraph, Last Sentence

With the implementation of amendment 04, transfer of ECG data to a central facility is no longer required.

Section 7.3.4.2. Echocardiogram or Multigated Acquisition Scan

Rationale for Change: Specific assessments, for purposes of the study, are being removed. Transfer of data to a central reader, for purposes of the study, is no longer required.

Revised text:

Last Paragraph, Last Sentence

With the implementation of amendment 04, transfer of scan data for independent cardiologist review is no longer required.

Section 7.4. Pharmacokinetics

Rationale for Change: Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

Revised text:

First Sentence

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

Section 7.5. Pharmacodynamics

Rationale for Change: Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

Revised text:

First Sentence

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

Section 7.6. Evaluation of Anti-Cancer Activity

Rationale for Change: Specific assessments, for purposes of the study, are being removed. Transfer of data to a central reader, for purposes of the study, is no longer required.

Revised text:

First Paragraph

With the implementation of amendment 04, CT, MRI, and Bone scan data will no longer be required for disease assessment, and samples for PSA ad CTC-ENU will no longer be collected. See the Time and Events Table (Section 7.1) for the updated schedule of assessments. Disease assessment should be managed according to local standard of care.

Section 7.6.3. Radiographic Response per PCWG3 Criteria

Rationale for Change: Specific assessments, for purposes of the study, are being removed. Transfer of data to a central reader, for purposes of the study, is no longer required.

Revised text:

Paragraph 2

With the implementation of amendment 04, transfer of scans to a central facility is no longer required.

Section 7.7.2. Tumor Tissue

Rationale for Change: Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

Revised text:

First Sentence

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

Section 7.7.3. Circulating Tumor Cells

Rationale for Change: Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

Revised text:

First Sentence

With the implementation of amendment 04, blood samples for CTC enumeration will no longer be collected.

Section 7.7.4. Circulating-Free Tumor DNA/RNA and Soluble Markers

Rationale for Change: Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

Revised text:

First Sentence

With the implementation of amendment 04, blood samples for cfDNA and soluble markers will no longer be collected.

Section 7.8. Genetics

Rationale for Change: Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

Revised text:

First Sentence

With the implementation of amendment 04, if a subject has consented for PGx research but the sample has yet to be collected, this will no longer be required.

Section 7.9.1. PRO-CTCAE

Rationale for Change: Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

Revised text:

First Sentence

With the implementation of amendment 04, the PRO-CTCAE will no longer be completed.

Section 7.9.2. EORTC-QLQ-C30, EORTC-QLQ-PR25 & Brief Pain Inventory – Short Form (BPI-SF)

Rationale for Change: Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

Revised text:

First Sentence

With the implementation of amendment 04, the quality of life questionnaires will no longer be completed.

Section 9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

Rationale for Change: 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. Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden. Any changes to the planned analyses for the study will be addressed in the Reporting Analysis Plan (RAP).

Revised text:

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).