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Division	:	Worldwide Oncology Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for 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
Effective Date	:	22-JUNE-2020

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the primary Clinical Study Report for Protocol 204697
- This RAP is intended to describe the planned safety, pharmacokinetics and efficacy analyses required for the interim analysis.
- This RAP will be provided to the study team members to convey the content of dose escalation, data reviews and interim analyses deliverables as well as the Statistical Analysis Complete (SAC) content.

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol: 204697

Revision Chronology:		
Original	13-OCT-2016	2015N238310_00
Amendment No. 1	01-FEB-2017	2015N238310_01
Amendment No. 2	08-FEB-2018	2015N238310_02
Amendment No. 3	12-JUL-2018	2015N238310_03
Amendment No. 4	06-MAY-2020	2015N238310_04

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There are no changes to the protocol defined statistical analysis as per the latest protocol amendment.

2.2. Study Objective(s) and Endpoint(s)

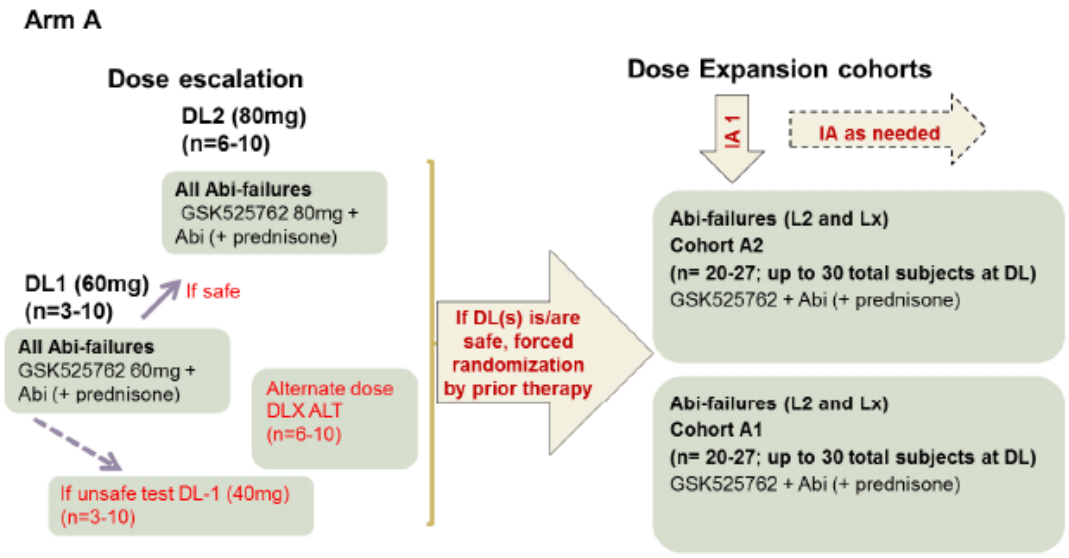
Objectives	**Endpoints**
Co-Primary (Both Arms)	**Co-Primary Endpoints**
• To determine the safety and tolerability of GSK525762, when given in combination with either abiraterone (Arm A) or enzalutamide (Arm B) in men with castration-resistant prostate cancer (CRPC)	• For both arms, adverse events (AEs), 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 recommend Phase 2 dose (RP2D) of GSK525762, when given in combination with either abiraterone (Arm A) or enzalutamide (Arm B) in men with 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 prostate-specific antigen [PSA] from baseline)
Secondary (Both Arms)	**Secondary Endpoints**
• To characterize the pharmacokinetics (PK) or exposure of GSK525762 and selected metabolites, when given in combination with abiraterone or enzalutamide, in men with (metastatic Castration-Resistant Prostate Cancer) CRPC	• PK parameter or concentration values for GSK525762 and selected metabolites following repeat-dose oral administration in combination with abiraterone or enzalutamide
• To characterize the PK or exposure of abiraterone or enzalutamide, when given in combination with GSK525762, in men with CRPC	• PK parameter or concentration values for abiraterone or enzalutamide following repeat-dose oral administration in combination with GSK525762

Objectives	Endpoints
• 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 Prostate Cancer Working Group (PCWG3)-modified Response Evaluation Criteria In Solid Tumours (RECIST) 1.1, b) PSA decrease of ≥50% at week 12 and thereafter, or c) circulating tumour cells CTC count conversion • Objective Response Rate (ORR) defined as complete response (CR) and partial response (PR) rate per PCWG3-modified (RECIST) 1.1 • Circulating Tumor Cells (CTC) response rate defined as percent of subjects having favourable (CTC<5/7.5mL) at nadir, if baseline is unfavourable 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 RECIST 1.1
• 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)	**Exploratory Endpoints**
• 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 (Bromodomain and ExtraTerminal) BET inhibition and (Androgen Receptor) AR signalling in tumour 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 tumour genomic deoxyribonucleic acid (DNA), protein and/or transcription ribonucleic acid (RNA) profiles with response. Correlate circulating biomarkers (e.g. AR-V7) with response

Objectives	Endpoints
• To describe the kinetics of tumour growth in the presence of GSK525762 for each treatment and investigate the relationship between tumour growth kinetics and clinical activity	• Tumour size or PSA levels over time, tumour growth rate constants, and time to tumour growth (TTG) predicted with the model parameters and relationship with clinical activity parameters.

2.3. Study Design

Overview of Study Design and Key Features



• 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

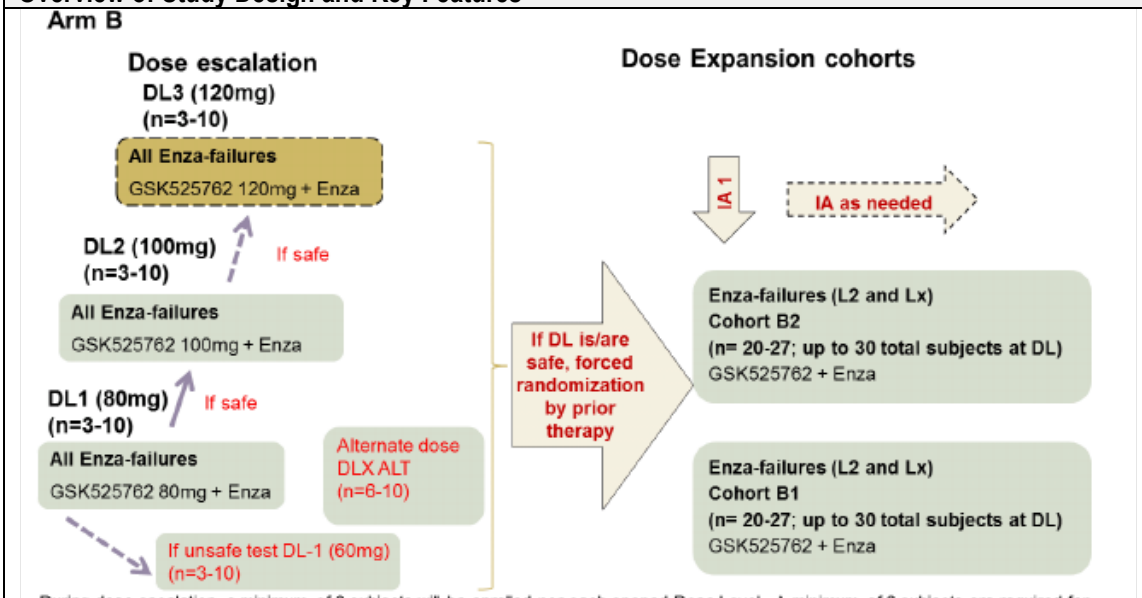
• IA: interim analysis to stop the arm with very low predictive probability of success on efficacy. May occur after first 10 evaluable subjects per DL. Additional IAs can occur every 10 evaluable subjects. Cohorts may be stopped at any time for futility.

• 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

Overview of Study Design and Key Features



- 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

Design Features	• This study is a two arm open-label Phase IB dose escalation and dose expansion study with oral administration of GSK525762 in combination with either abiraterone (Arm A) or enzalutamide (Arm B) in male subjects with CRPC 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, treatment arms will follow a modified toxicity probability interval (mTPI) design which 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 centred 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). • 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. The first interim analysis will be conducted for each individual dose and it may be conducted when at least 10 evaluable subjects are

Overview of Study Design and Key Features	
	available for a given dose. After the first interim analysis, interim analyses can be conducted after every 10 additional subjects become evaluable. **Arm A** • In Arm A, eligible subjects with CRPC 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-naïve or chemo-treated), but the most recent treatment before enrolment into Arm A must be abiraterone. • 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. 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. • Once dose escalation phase and dose selection are complete, a total of 30 subjects each may be enrolled into both selected dose expansion cohorts, including dose escalation subjects, and approximately 10 enrolled subjects will be L2 and 20 subjects will be Lx. **Arm B** • In Arm B, eligible subjects with CRPC 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. • 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 Drug Drug Interaction (DDI). If DL80 does not exceed the MTD, dose level 100 mg (DL100) (GSK525762 given 100 mg QD) will be opened. 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. • Once dose escalation phase and dose selection are complete, a total of 30 subjects each may be enrolled into both each selected dose expansion cohorts, including the dose escalation subjects, and approximately 10 enrolled subjects will be L2 and 20 subjects will be Lx.
Dosing	**Dose Escalation:** • For Arm A, projected dose levels of GSK525762 are 60 mg and 80 mg administered once daily. Due to emerging data (safety/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 an alternate/intermittent dosing at 60mg dose level (DL60 ALT) and/or a lower daily dose level (DL-1, 40 mg) may be evaluated. • For Arm A, for subjects receiving GSK525762 in combination with abiraterone, daily administration of combination therapy (GSK525762 and abiraterone) will commence

Overview of Study Design and Key Features	
	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. Based on emerging information collected from PK, PD and safety/tolerability data, other dosing regimens (such as twice daily (BID) dosing for both drugs or intermittent dosing for GSK525762 or staggered dosing of the two drugs) may be explored during the study. • 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 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 (120 mg Dose Level) 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. • For Arm B, for subjects receiving GSK525762 in combination with enzalutamide, daily administration of combination therapy (GSK525762 and 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. 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. • Dose levels of abiraterone and enzalutamide are as approved 1000 mg and 160 mg respectively, administered once daily. No doses will be explored beyond 1000 mg abiraterone or 160 mg enzalutamide, these doses 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. **Dose Expansion:**

Overview of Study Design and Key Features	
	• 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
Time & Events	• Refer to Section 13.2 (Appendix 2: Schedule of Activities)
Treatment Assignment	• Subjects will be assigned to receive GSK525762 and abiraterone/enzalutamide in an open-label fashion. • This study will consist of dose escalation and dose expansion cohorts. An 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 approximately 1/3 of the subjects from L2 and 2/3 of the subjects from Lx: - GSK525762 at RP2D+enzalutamide (Arm B).
Interim Analysis	**Dose escalation data reviews:** • For each dose level, once 3 to 6 subjects have been enrolled at each dose level for each arm, an interim data review will be performed to determine if dose-escalation, dose de-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. **Dose Expansion interim analyses:** • 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. After the first interim analysis, the interim analysis can be conducted after every 10 additional subjects become evaluable i.e., have had the week 12 PSA results or have progressed or died or permanently withdrawn from the study treatment. • Enrolment may be stopped early in any of the expansion cohorts for toxicity or lack of efficacy.
Final Analysis	• 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. • Data from the dose escalation and expansion cohort will be combined as appropriate.

2.4. Statistical Hypotheses / Statistical Analyses

2.4.1. Dose escalation

For dose escalation, no formal statistical hypotheses will be tested. Decisions on determining the recommended dose for further exploration will be based upon safety, PK and efficacy profiles of GSK525762 plus abiraterone or enzalutamide in subjects with CRPC.

2.4.2. Dose expansion cohorts

For dose expansion, the efficacy endpoint is defined as the response rate (% of subjects achieving PSA reduction from baseline ≥50%) at 12 weeks and/or thereafter for the subjects treated at each dose level. A response rate of 30% or greater is desired while 10% represents a response rate that is clinically unacceptable.

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). 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 also at the 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.

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 dU is greater than the clinically significant minimum utility (CSMU) at interim for each dose.

The first interim analysis will be conducted for each cohort and it may be conducted when at least 10 evaluable subjects are available for a given cohort. After the first interim analysis, the interim analyses may 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 each interim futility analysis in each expansion cohort, the enrolment for that cohort may be stopped due to futility if the posterior probability that the 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 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 dose levels. The difference of PSA RR, 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 may be recommended as RP2D for each combination, respectively.

3. PLANNED ANALYSES

3.1. Interim Analyses

Formal interim futility analyses will be performed based on a Bayesian adaptive design. Details are provided in Section 3.1.2

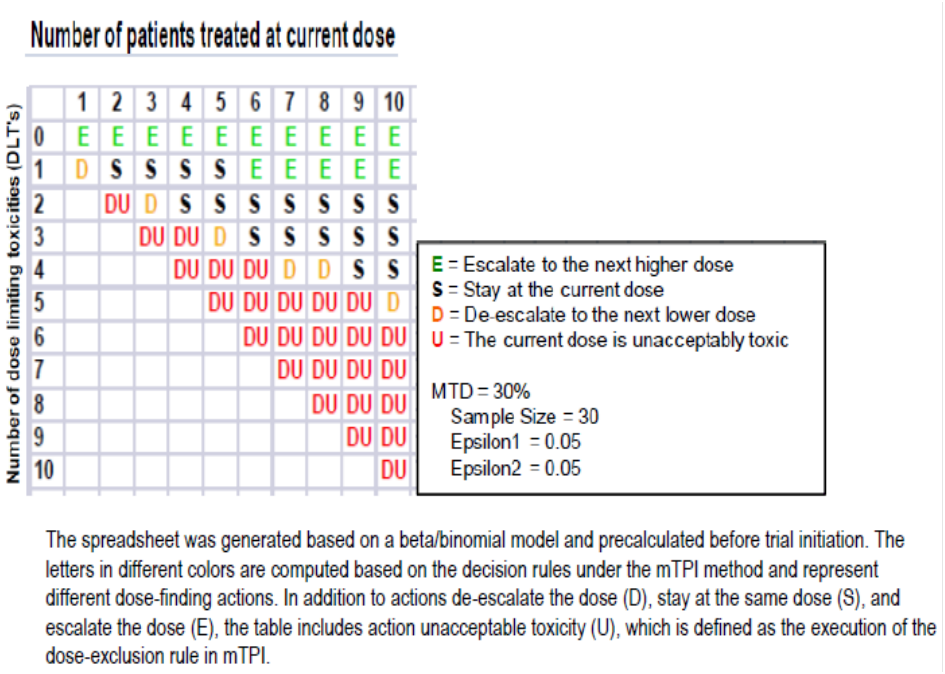
3.1.1. Dose Escalation Phase

Once 3 to 6 subjects have been enrolled at each dose level, a data review 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. The analysis will be based on Modified All Treated Population.

The mTPI design rules together with the predicted dose-limiting toxicity rates at all dose levels will lead the decision to determine whether dose escalation and expansion will be continued as planned. 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 and enzalutamide falls within the rage from 25% or 35% and centred at 30%. 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.

The monitoring rules guiding dose escalation are provided below. 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 (E), staying at the same dose (S) and de-escalating the dose (D). 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 subject 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 experience toxicity, the decision is at row 0 and column 3, which is E – 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 experience toxicity, the decision is DU – to de-escalate to the next-lower doe level and exclude the current dose from the trial, because the high toxicity level is unacceptable.

Figure 1 Modified toxicity probability interval (mTPI) method dose finding rules



	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 with up to 10 additional subjects to further evaluate safety, pharmacokinetic and tolerability before dose escalation or reduction decision is determined.

3.1.1.1. Displays To Be Created For Dose Escalation Review

Review of preliminary data will be performed after 3-10 subjects complete the DLT evaluation period of 28 days for each dosing level.

For the first dose escalation meeting, spreadsheets containing relevant study data will be supplied by the study data manager. For dose escalation meetings after the first cohort, SDTM datasets will be uploaded and made available in Spotfire. Both GSK and PAREXEL personnel will have access to Spotfire and can view subject-level data in Spotfire.

The PK samples will be analysed for GSK525762 and metabolite after more than three subjects are enrolled and PK samples obtained up to Week 3 Day 1.

Prior to determining a dose for the next cohort, exploratory analyses may be conducted to assess the relationship of dose level with safety, PK, and pharmacodynamic parameters using all data from available cohorts.

The GSK study team, in collaboration with study investigators and the PAREXEL study team, will review all relevant data to support:

- whether the current dose had acceptable toxicity, and
- the decision regarding the next dose level based on the totality of the data

For further details see 230779 Dose Escalation Plan 20171102 V1.0 (230779_Dose_Escalation_Plan_20171102_V_1.0).

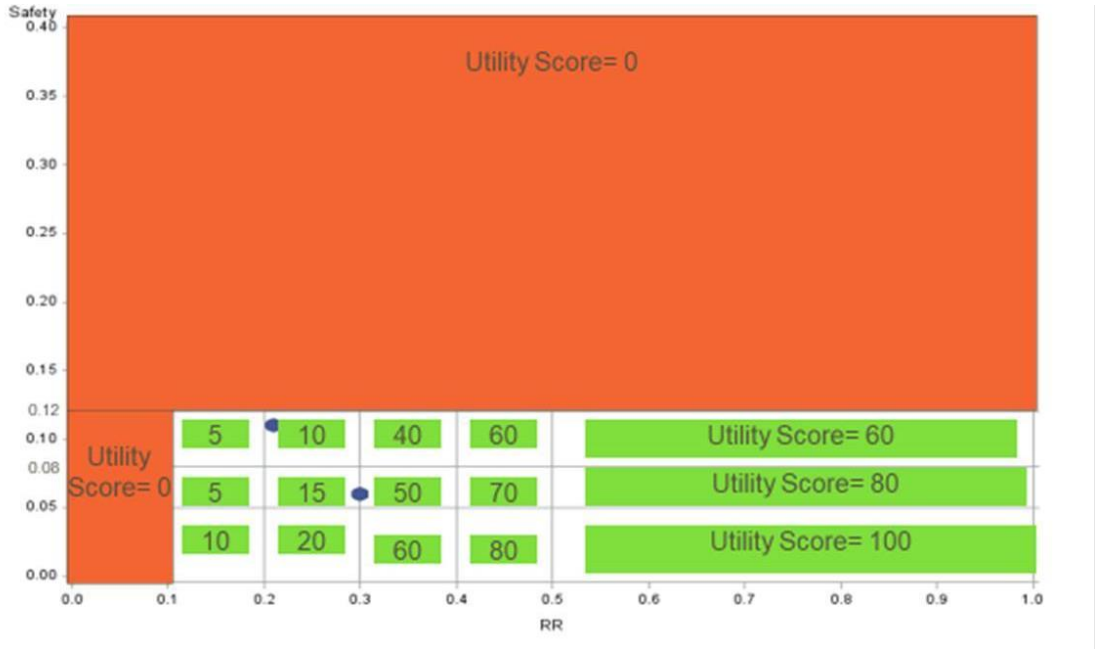
3.1.2. Dose Expansion Phase

Interim analyses for futility will be conducted for each expansion cohort when at least 10 evaluable subjects are available for a given cohort. Additional interim futility analyses may be conducted after every 10 additional subjects become evaluable (refer to Section 4 for definition of evaluable subjects). Enrolment may be stopped early in any of the expansion cohorts for toxicity or lack of efficacy, using a utility function that is a combination of response rate and the dose modification rate. 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.

Data from evaluable subjects treated in the dose escalation cohorts will be analysed together with expansion cohort subjects treated at the same dose and schedule in the same combination for futility analysis.

The PSA response rate (RR) (see definition Section 7.1) and dose modification rate will be jointly assessed using a utility function. For each expansion cohort the *dU* will be calculated and used for decision making at each futility analysis. For each futility analysis in each expansion cohort, the enrolment for that cohort may be stopped due to futility if the posterior probability that the dU > CSMU (25) is small (less than a 4% chance for the utility to be larger than the CSMU). The totality of the data including safety/tolerability, primary and secondary efficacy endpoints will be used to decide whether to stop enrolment within a cohort at an interim analysis. The utility function mapping given safety and efficacy measures is given below:

Figure 2 Utility Function Mapping



Utility function is greater than 25 when RR is greater than 0.3 and safety (dose modification rate) is less than or equal to 0.12. Since it is assumed that DLT rate 0.1, 0.3 and 0.4 will have dose modification rate R=0.05, 0.08 and 0.12 respectively the DLT rate can be used for safety and instead of using 0.12, we have used 0.4 for the DLT rate. Therefore, assuming independence of the safety and efficacy (RR) endpoints, we can calculate the posterior probability of the dU > CSMU (25) by:

Posterior probability true DLT rate (p_1) ≤ 0.4 multiplied by posterior probability true RR (p_2)> 0.3 for each dose level in the dose expansion phase.

Posterior probabilities will be calculated using the following assumptions:
Observed data: $\#\ of\ DLTs \sim Bin\ (n, p_1)$
Prior distribution of p_1: $p_1 \sim Beta\ (0.0001, 0.0001)$
Posterior distribution of p_1 given observed data:

$$p_1|\#\ DLT \sim Beta(0.0001 + \#\ of\ DLTs, 0.0001 + n - \#\ of\ DLTs\ )$$

Observed data: $\#\ of\ RRs \sim Bin\ (n, p_2)$
Prior distribution of p_2: $p_2 \sim Beta\ (0.0001, 0.0001)$
Posterior distribution of p_2 given observed data:

$$p_2|\#\ RR \sim Beta(0.0001 + \#\ of\ RRs, 0.0001 + n - \#\ of\ RRs\ )$$

- Posterior probability true DLT rate (p_1) $\leq$ 0.4: Area under the $Beta(0.0001 + \#\ of\ DLTs, 0.0001 + n - \#\ of\ DLTs\ )$ curve, to the left of 0.4.
- Posterior probability true RR (p_2) > 0.3: Area under the $Beta(0.0001 + \#\ of\ RRs, 0.0001 + n - \#\ of\ RRs\ )$ curve, to the right of 0.3.

Multiplying these probabilities will give the posterior probability that the true dU > 25.

Posterior probabilities for each endpoint (DLT, RR) will be summarised together with the utility by dose.

3.1.2.1. Displays for dose expansion Interim Analyses

The study population of Modified All Treated subjects will be used for efficacy analyses at interim. As subjects enrol at different times, not all subjects will have been on the study long enough to have single or multiple disease assessments.

The Modified All Treated population will be used to produce subject disposition, study population, demographics and safety summaries, unless otherwise specified.

RR is defined as the proportion of participants with a PSA reduction from baseline ≥ 50% is observed at 12 weeks or later (must be confirmed by a second value).

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. Summaries of confirmed response rate will be provided for the study team to compare study data to the stopping rules for futility.

A listing of subject status and PSA response will be provided. This listing will be sorted by date of first dose within a subject and will show whether each subject is ongoing with

study treatment, whether the subject is evaluable for the futility analysis, maximum PSA decline and PSA response. Another listing on subject best response will be provided that will include whether the subject had measurable disease at baseline, best radiological response and bone progression.

PSA RR, DCR (confirmed), CRR (confirmed), ORR (confirmed and unconfirmed), CTC response rate, and Week 4 PSA response rate will be summarised along with 95% exact confidence interval.

Safety outputs will be generated for the interim analysis with summaries of exposure to GSK525762 and enzalutamide, summaries of adverse events and serious adverse events by system organ class and preferred terms as well as. Summaries of any drug-related, GSK525762-related and enzalutamide-related adverse events and summary of adverse events of special interest will also be presented.

Data from both dose escalation and the expansion cohorts will be reported by arm and L2 vs. Lx (cf. definition Section 5.5.1) subgroups when appropriate. A full list of displays can be found in Appendix 10.

3.2. Final Analyses

Final analysis is planned when the last subject enrolled has had the opportunity to be followed for 6 months in order to allow for maturity of 24 week DCR endpoint maturity. Data from the dose escalation and expansion cohort will be combined as appropriate and reported by study dose for each arm and L2 vs. Lx (see definition on Section 5.5.1) subgroups when appropriate.

The final analysis will be performed after all required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management. As final analysis will be performed at a time when some patients may still be on follow-up and more data may become available at the time of study closure an amendement to this RAP will be performed if needed allowing for a re-run of the analysis described below.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Screened Population	• Subjects who consent to participate in the trial	• Screen failures
All Treated Population	• All subjects who receive at least one dose of GSK525762 or abiraterone or enzalutamide.	• Safety • Anti-cancer activity • Study population
Modified All Treated Population	• All subjects who receive at least one dose of GSK525762 plus abiraterone or enzalutamide.	• Efficacy • Safety (if different from the All Treated population.)

Population	Definition / Criteria	Analyses Evaluated
		• Anti-cancer activity (if different from the All Treated population.) • Value Evidence Outcomes
All Evaluable Population	• All subjects who have had Week 12 or later visit disease assessment results or have progressed or died or permanently withdrew from the study treatment will be included in this population.	• Dose escalation Phase only
PK Population	• All subjects from the Modified All Treated Safety Population for whom a PK sample is obtained and analysed.	• PK analysis

NOTES: Please refer to Appendix 10: List of Data Displays which details the population to be used for each display being generated.

4.1. Protocol Deviations

Major protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and all protocol deviations will be listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Specifications developed by PAREXEL.

- Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the electronic case report form (eCRF). As there is no Per-Protocol Population for this study, protocol deviations will not be used to determine membership in any particular study population for this study.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Data will be listed and summarised according to the GSK reporting standards, where applicable. Data will be listed and summarised mostly by dose levels and by each study part and/or combined (wherever applicable).

5.1. Study Treatment & Sub-group Display Descriptors

Data will be summarised and listed according to GSK reporting standards, as applicable. All data displays (Tables, Figures & Listings) will use the term "Subject" which reflects Clinical Data Interchange Standards Consortium (CDISC) and GSK Data Display Standards terminology. Tables, figures and listings will be displayed by treatment doses. Actual study treatment doses will depend on the outcome of the dose escalation phase but will follow the same format. Subgroups described in Section 5.5.1 may also be used in summaries.

Treatment Group Descriptions		
IRT System	**Data Displays for Reporting**	
Description	**Treatment Label**	**Order in TLF**
Arm A		
A DL 1 60mg	GSK762 60mg + Abi 1000mg	1
A DL 1 60mg ALT	GSK762 60mg Alt + Abi 1000mg	2
A DL -1 40mg	GSK762 40mg + Abi 1000mg	3
Arm B		
B DL 1 80mg	GSK762 80mg + Enza 160mg	4
B DL-1 60mg	GSK762 60mg + Enza 160mg	5
B DL-1 60mg ALT	GSK762 60mg Alt + Enza 160mg	6

NOTES: Order represents treatments being presented in TFL, as appropriate.

5.2. Reporting Conventions

- Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of subjects with non-missing value at each visit.
- All data are reported per the dose/regimen initially received by the subject.
- Unless stated otherwise, descriptive summaries will include n, mean, standard deviation, median, minimum and maximum for continuous variables and n and percent for categorical variables. Display minimum and maximum in the same precision as data was collected, mean and median using 1 additional decimal place, and standard deviation using 2 additional decimal places.
- At a minimum, data will be listed by treatment group, centre ID, and subject ID.
- Planned times relative to investigational product dosing will be used in all summary tables and figures unless otherwise specified.
- Unscheduled visits will be included in the listing using actual time and will be used in deriving the maximum or minimum value over time (e.g. worst-case value post dose). However, unscheduled visits will not be included in summaries by planned time.

- Actual, rather than planned, sampling times will be used in the derivation of PK parameters and in the individual concentration-time plots. Planned times will be used in the descriptive summaries and in mean and median plots. Listings of PK concentration-time data will be done by actual sampling times relative to dosing time.
- No formal assessment windows will be defined for the purpose of classifying measurements obtained outside of scheduled assessment times.
- This is a multicentre study. Data from all study sites will be integrated and no controlling for centre-effect will be considered in the statistical analyses.
- Analyses are to be performed using the SAS System, Version 9.4 or higher. Programs will be imported into HARP and the final output will be produced by running drivers in HARP. Some graphics may be produced using the TSCG (Tibco Spotfire Clinical Graphics) - comprising of S-Plus (R) 7.0.6 or higher.
- Deviations from the analyses in the RAP will be identified in the final clinical study report (CSR).

5.3. Baseline Definitions

For all endpoints, baseline will be defined as the most recent (latest), non-missing assessment time-point prior to the first study treatment dose.

For enrolled subjects who did not receive study treatment during the study, baseline will be defined as the latest non-missing assessment time-point providing analysable data.

For laboratory data, baseline will be defined as the most recent, non-missing value from a central laboratory prior to the first study treatment dose. If there are no central labs collected for a subject, the most recent, non-missing value from a local laboratory prior to the first dose of study treatment will be defined as the baseline value.

For ECG analyses, the baseline value will be represented by the mean of the triplicate of the most recent (latest) assessment time-point prior to the first study treatment dose if available. If Fridericia's QT Interval Corrected for Heart Rate (QTcF) results are not available at baseline, then the mean of the screening triplicate QTcF results will be used.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

Parameter	Study Assessments Considered as Baseline		Baseline Used in Data Display
	Screening	Day 1 (Pre-Dose)	
Efficacy			
PSA	X	X	Latest up to Day 1
CT	X		Latest up to Screening
MRI	X		Latest up to Screening
Bone scan	X		Latest up to Screening
CTC	X	X	Latest up to Day 1
Safety			
Laboratory	X	X	Latest up to Day 1
Performance Status	X	X	Latest up to Day 1
Vital Signs	X	X	Latest up to Day 1
ECG* (QTc)	X	X	Latest up to Day 1
ECHO/MUGA (LVEF, …)	X		Latest up to Screening
Liver Events	X	X	Latest up to Day 1
PRO-CTCAE	X	X	Latest up to Day 1
Value Evidence Outcomes			
EORTC-QLQ-C30	X	X	Latest up to Day 1
EORTC-QLQ-PR25	X	X	Latest up to Day 1
BPI-SF	X	X	Latest up to Day 1
PRO-CTCAE	X	X	Latest up to Day 1

*Average of triplicate assessments to be used if available.

5.3.1. Change from baseline

For records occurring after baseline change from baseline is calculated as: (visit value) – baseline value.

For records occurring after baseline percent change from baseline is calculated as: ((change from baseline) / baseline value) * 100

If either the baseline or visit value is missing, the change from baseline and/or percent change from baseline is set to missing.

5.3.2. Multiple Assessments

All data will be reported according to the nominal visit date for which it was reported (that is, no visit windows will be applied during dataset creation). Unscheduled data will only be included in the display sections that report worst- case post-baseline. For summaries that collapse data across multiple planned time intervals, select the mean data at each collapsed interval.

With the exceptions of ECG and echocardiogram (ECHO/MUGA) assessments, if multiple assessments of the same type were performed on different days but reported for the same

scheduled assessment, then the worst-case assessment for that scheduled assessment will be analysed.

With the exceptions of laboratory, ECG, and ECHO/MUGA assessments if multiple assessments of the same type are reported on the same date for the same scheduled planned time, then the mean of multiple measurements reported for the same date will be analysed. When data could be reported from both central and local laboratories and if laboratory data is reported from both central and local laboratories with the same date, then the central laboratory data will be analysed to provide consistency with measurements from other subjects. As a general rule for ECG and ECHO/MUGA only the post-baseline assessments that used the same method (i.e. Electrocardiogram ECHO or Multiple Grated Acquisition MUGA) and the same source (i.e. local or central cardiologist read) as the baseline assessments will be used to derive the change from baseline, data from the two sources will not be combined.

Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings.

5.4. Multicentre Studies

Data from all participating centres will be pooled prior to analysis. It is anticipated that subject accrual will be spread thinly across centres and summaries of data by centre would be unlikely to be informative and will not, therefore, be provided.

5.5. Examination of Subgroups

5.5.1. Covariates and Other Strata

No covariate-adjusted or stratified analyses are planned for this study.

5.5.2. Examination of Subgroups

Subject subgroups to be included in analysis and reporting may be represented by prior line of therapy L2 (failed first line treatment with or without one prior line of chemotherapy) versus Lx (on re-treatment after failure of multiple lines of therapy including prior ADT/prior chemotherapy/prior radiation therapy) for efficacy and safety outputs for both arms.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
13.3	Appendix 3: Assessment Windows
13.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
13.5	Appendix 5: Data Display Standards & Handling Conventions

Section	Component
13.6	Appendix 6: Derived and Transformed Data
13.7	Appendix 7: Reporting Standards for Missing Data
13.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the All Treated population, unless otherwise specified. Study population summaries will include descriptive summaries and data listings of subject disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, prior and concomitant anti-cancer therapies based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 10: List of Data Displays.

6.2. Disposition of Subjects

A summary of the number and percentage of subjects in each of the analysis populations (described in Section 4) and numbers and percentages of exclusions from each population will be provided. A listing of subjects excluded from analysis populations will also be provided, and both a summary and a listing of subject screening status and reasons for screen failure will be provided. A listing of run-in failures will also be provided.

A summary of study treatment status will be provided. This display will show the number and percentage of subjects who are ongoing or discontinued study treatment and a summary of the primary reasons for discontinuation of study treatment. Reasons for study treatment discontinuation will be presented in the order they are displayed in the eCRF. A listing of study treatment discontinuation will be generated. The listing will include last dose date, and reasons for study treatment discontinuation

A summary of subject status and reason for study withdrawal will be provided. This display will show the number and percentage of subjects who completed the study and those withdrew from the study, including primary reasons for study withdrawal. Reasons for study withdrawal will be presented in the order they are displayed in the eCRF. A listing of reasons for study withdrawal will also be included.

6.3. Protocol Deviations

Only major protocol deviations will be summarised, whereas all protocol deviations (regardless of the categorisation) will be listed including inclusion/exclusion deviations as well as other deviations. Protocol deviations will be classified as ‘major’ and ‘minor’ based on Protocol Deviation Specifications.

6.4. Demographic and Baseline Characteristics

Demographic and other baseline characteristics of subjects (e.g., age, race, ethnicity, sex, and body height and weight) will be both summarised and included in a listing. Age, height, weight will be summarised as continuous variables using the mean, standard deviation, minimum, median and maximum whereas sex, race, and ethnicity will be summarised as categorical variables. In addition, age will also be categorized and summarised by the EudraCT categories of 18-64, 65-84 and ≥85 years and GSK IDSL categories of <18, 18-64, and ≥65 years. A separate listing dedicated to categorical age and both a separate summary and listing dedicated to race/racial combinations will also be provided.

Disease history and characteristics at initial diagnosis and study screening will be separately summarised; as appropriate per summary, characteristics may include primary tumour type, stage, lesion status, time since initial diagnosis in months, stage at initial diagnosis, time since latest disease progression (in weeks), method by which progression was determined (Biochemical Progression, Radiological Progression – Bone Lesion or Radiological Progression – Viceral Lesion) on prior disease progression, screening, visceral status. Separate summaries of disease characteristics at initial diagnosis and screening will be provided. A summary of disease burden at baseline including sites of metastatic disease will be produced. Information on sites of metastatic disease at screening will also be listed.

Medical conditions present at screening will be separately summarised by past and current categories; both past and current conditions will be disclosed in a single listing. Medical conditions that are not pre-specified will be incorporated into the listing only.

Substance use, including history of smoking, tobacco, and alcohol, will be disclosed in a listing.

Prior anti-cancer therapy will be coded using the GSK drug coding dictionary. Separate summaries of prior anti-cancer therapy will be dedicated to all therapies (including radiotherapies), prior dictionary-coded therapies, and number of therapy regimens. A summary of best response to most recent prior anti-cancer therapy will be provided.

Prior and post-treatment cancer-related surgeries will be included in the same listing.

The details of the planned displays are provided in Appendix 10.

6.5. Concomitant Medications

Concomitant medications will be coded using GSK Drug coding dictionary, summarised and listed. The summary will show the number and percentage of subjects taking concomitant medications by ingredient. Multi-ingredient products will be summarised by their separate ingredients rather than as a combination of ingredients. Anatomical-Therapeutic-Chemical (ATC) Level 1 (Body System) classification will be included in the created dataset but will not appear in the summary table or listing.

In the summary of concomitant medications, each subject is counted once within each unique ingredient. For example, if a subject takes Amoxycillin on two separate occasions, the subject is counted only once under the ingredient ‘Amoxycillin’. In the summary of concomitant medications, the ingredients will be summarised by the base only. A single listing, incorporating both blood products and supportive care products, will be provided.

Note that, in order to be considered a concomitant medication, the concomitant medication must have been taken at some point during the on-therapy window.

7. EFFICACY ANALYSES

The efficacy analyses will be based on the Modified All Treated population, unless otherwise specified. All analyses will be presented by dose level for each arm. A subgroup analysis by number of lines of prior therapy (L2 vs. Lx) may also be provided.

7.1. Primary Efficacy Analyses

7.1.1. PSA Response Rate (RR)

The primary efficacy endpoint is PSA RR. It 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 (±5 days) after start of treatment and confirmed ≥ 4 weeks later by an additional PSA evaluation.

7.1.2. Summary Measures

Only subjects who have a baseline PSA value will be included in the analysis of PSA response. Subjects without any assessment at 12 weeks or after will be included in the denominator for the calculation of PSA RR.

Response rate (confirmed) will be summarised for each dose level for each arm along with exact 95% confidence interval. A subgroup analysis for response rate by number of lines of prior therapy (L2 vs. Lx) will also be provided.

Waterfall plots will be provided for maximum reduction in PSA value and maximum percentage of change in PSA from baseline. In addition, spider plots with PSA percent change from baseline over time will be provided for all subjects.

Absolute values of PSA and its change from baseline in percentage will be listed.

7.1.3. Population of Interest

The primary efficacy analysis will be based on the Modified All Treated population.

7.1.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints/variables defined in Section 7.1.1 will be summarised using descriptive statistics, graphically presented (if appropriate), and listed.

Primary Statistical Analyses
Endpoint(s)
RR

Primary Statistical Analyses
Method of Analysis
Exact 95% CI

7.2. Secondary Efficacy Analyses

7.2.1. Endpoint / Variables

7.2.1.1. Disease Control Rate at 24 weeks (DCR)

The DCR is defined as the proportion of subjects with confirmed PR or CR or a SD at ≥ 24 weeks (minimum 163 days to account for visit window).

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).

7.2.1.2. Time to Disease Progression

Time to disease progression is defined as the time from date of first dose of study treatment to date of 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 PCGW3 criteria
- PSA progression according to the PCWG3 criteria accompanied by any one of the following: investigator-defined clinical progression or either of the above RECIST 1.1 radiographic progression or bone progression

Subjects without disease progression at the time of analysis or that died will be censored at the date of the latest PSA assessment and latest radiological assessment. If a patient dies or starts new anti-cancer therapy, then they will be censored at latest date of last PSA assessment and last radiological assessment on or prior to new anti-cancer therapy or date of death.

7.2.1.3. Objective Response Rate (ORR)

The ORR is defined as the percentage of subjects with a confirmed CR or a PR at any time as per PCWG3- modified RECIST 1.1.

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.

7.2.1.4. Circulating Tumour Cells (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) for subjects with unfavourable (≥5/7.5mL) CTC at baseline.

Subjects with CTC<5/7.5 mL at baseline will be excluded from this analysis.

7.2.1.5. Composite Response Rate (CRR)

CRR is a composite endpoint based on the following:

- Response based on PCWG3 modified RECIST 1.1
- PSA decrease of ≥50% from baseline at Week 12 or thereafter
- CTC count conversion from unfavourable (>=5/7.5mL) at baseline to favourable (<5/7.5mL) confirmed by a second assessment at least 4 weeks later.

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. If a subject meets at least one of the above requirements, then that subject will be considered a composite responder.

Subjects with unconfirmed response per PCWG3-modified RECIST 1.1 will be classified as non-responders.

7.2.1.6. PSA Week 4 Response Rate (Week4 RR)

Week 4 RR is defined as the proportion of participants with a PSA reduction from baseline ≥ 30% observed at 4 weeks.

7.2.1.7. Radiographic Progression-free survival (rPFS)

rPFS will be defined as the time from date of first dose of study treatment until the first date of either radiographic disease progression or death due to any cause whichever occurs first. The date of disease progression will be defined as the earliest date of disease progression as assessed by the investigator using PCWG3-modified RECIST 1.1 or progression on bone scan. For subjects who have not progressed or died at the time of 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 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.

7.2.2. Summary Measure

7.2.2.1. Disease Control Rate (DCR)

The number and types of responses (confirmed), as outlined in PCWG3-modified RECIST 1.1, will be listed and summarised separately, as appropriate. The estimate of DCR along with an exact two-sided 95% confidence interval (CI) will be provided for each dose level and cohortspecified.

A subgroup analysis by number of lines of prior therapy (L2 vs. Lx) may also be provided.

7.2.2.2. Time to Disease Progression

Time to disease progression will be summarised using Kaplan-Meier methods including estimates and 95% CI for medians and quartiles based on a g-transformed confidence interval for S(t) where g is linear (Klein and Moeschberger method) for each dose level specified.

A subgroup analysis by number of lines of prior therapy (L2 vs. Lx) may also be provided.

A summary of the assignments for progression and censoring dates for time to disease progression are specified in Table 1 below.

7.2.2.3. Objective Response Rate (ORR)

The observed ORR (confirmed) will be reported for each dose level. The estimates along with 95% exact two-sided confidence interval CI will be provided. All data related to response assessment from the Investigator will be listed including target lesion measurements, non-target lesion assessment, new lesion and response assessments.

A subgroup analysis by number of lines of prior therapy (L2 vs. Lx) may also be provided.

If CR or PR response are present in the data a waterfall plot of the maximum percent change in target lesions from baseline will be provided. The plot will be colour coded for best overall response with confirmation. In addition, spider plots of percent change from baseline in target lesions over time will be provided for each subject.

7.2.2.4. Circulating Tumour Cells (CTC) Response

CTC response rate will be presented along with an exact two-sided 95% confidence interval for each dose level. Percent change from baseline in actual cell counts will be summarised and listed by visit.

A subgroup analysis by number of lines of prior therapy (L2 vs. Lx) may also be provided.

Waterfall plots of maximum CTC percent change from baseline will also be presented. In addition, spider plots with CTC counts percent change from baseline over time will be provided for each subject.

7.2.2.5. Composite Response Rate (CRR)

The CRR (confirmed) will be reported for each dose level along with corresponding exact two-sided 95% CI.

A subgroup analysis by number of lines of prior therapy (L2 vs. Lx) may also be provided.

7.2.2.6. PSA Week 4 Response Rate (PSA Week4 RR)

Week 4 PSA RR will be reported along with the exact two-sided 95% CI for each dose level.

A subgroup analysis and a listing by number of lines of prior therapy (L2 vs. Lx) may also be provided.

7.2.2.7. Radiographic Progression-free survival (rPFS)

rPFS will be summarised by dose level using Kaplan-Meier quantile estimates along with two-sided 95% CI based on a g-transformed confidence interval for S(t) where g is linear (Klein and Moeschberger method) for each dose level, if data warrant.

Kaplan Meier curve will also be produced, if data warrant.

A subgroup analysis by number of lines of prior therapy (L2 vs. Lx) may also be provided.

A summary of the assignments for progression and censoring dates for rPFS are specified in Table 1 below.

Table 1 Assignments of Progression and Censoring Dates for Time to Disease Progression Analysis

Scenario	Date of Event (Progression/Death) or Censored	Event (Progression/Death) Or Censored
No adequate baseline assessments[2] and the subject has not progressed or died and has no PD (from RS (Response Dataset) or DS (Disposition Dataset))	First dose	Censored
No post-baseline assessments and the subject has not died and has no PD (from DS)	First dose	Censored
Progression prior to an anti-cancer therapy (Note this includes progression at baseline or without any adequate assessments)	Date of assessment of progression[1].	Event
With post-baseline assessment but no progression (or death) or anti-cancer therapy	Date of last 'adequate' assessment of response[2]	Censored
No adequate post-baseline assessment before start of new anti-cancer therapy without PD or prior to PD from DS	First dose	Censored
With adequate post-baseline assessment and new anti-cancer treatment started (without PD or prior to documented disease progression).[3]	Date of last 'adequate' assessment of response[2] (prior to starting anti-cancer therapy)	Censored
Death or progression from RS or DS (prior to anti-cancer therapy or no anti-cancer therapy) after two or more missed consecutive scheduled assessments	Date of last 'adequate' assessment of response[2] (prior to missed assessments) or first dose when there is no 'adequate' assessment[2] of response: (1) If the previous assessment is less than Day 274 and the difference between death/PD and last adequate assessment[2] is more than 126 days (2) If the previous assessment is between Day 274 and Day 344 and the difference between death/PD and last adequate assessment[2] is more than 154 days (3) If the previous assessment is greater than Day 344 and the difference between death/PD and last adequate assessment[2] is more than 182 days Note: The scheduled assessments are every 8 weeks up to 6 months, then every 12 weeks. The scheduled assessments windows are: ±7d.	Censored

[1] The earliest of (i) Date of radiological assessment showing new lesion (if progression is based on new lesion); or (ii) Date of radiological assessment showing unequivocal progression in non-target lesions, or (iii) Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)
[2] An adequate assessment is defined as an assessment where the Investigator determined response is CR, PR, or SD. Note it can be scheduled or unscheduled.
[3] If PD and New anti-cancer therapy occur on the same day assume the progression was documented first e.g., outcome is progression and the date is the date of the assessment of progression)

Table 2 Assignments of Progression and Censoring Dates for rPFS Analysis

Scenario	Date of Event (Progression/Death) or Censored	Event (Progression/Death) Or Censored
No adequate baseline assessments[2] and the subject has not progressed or died (if the subject has died follow the rules for death indicated at the bottom of the table) and has no PD (from RS or DS)	First dose	Censored
No post-baseline assessments and the subject has not died (if the subject has died follow the rules for death indicated at the bottom of the table) and has no PD (from DS)	First dose	Censored
Without anti-cancer or prior to an anti-cancer, progression/death (Note this includes progression/death at baseline or without any adequate assessments)	Date of assessment of progression[1] or date of death, whichever comes first.	Event
With post-baseline assessment but no progression (or death) or anti-cancer	Date of last 'adequate' assessment of response[2]	Censored
No adequate post-baseline assessment before start of new anti-cancer therapy without PD or prior to PD from DS	First dose	Censored
With adequate post-baseline assessment and new anti-cancer treatment started (without PD or prior to documented disease progression).[3]	Date of last 'adequate' assessment of response[2] (on or prior to starting anti-cancer therapy)	Censored
Death or progression from RS or DS (prior to anti-cancer therapy or no anti-cancer therapy) after two or more missed consecutive scheduled assessments	Date of last 'adequate' assessment of response[2] (prior to missed assessments) or first dose when there is no 'adequate' assessment[2] of response:	Censored

Scenario	Date of Event (Progression/Death) or Censored	Event (Progression/Death) Or Censored
	(1) If the previous assessment is less than Day 274 and the difference between death/PD and last adequate assessment[2] is more than 126 days (2) if the previous assessment is between Day 274 and Day 344 and the difference between death/PD and last adequate assessment[2] is more than 154 days (3) If the previous assessment is greater than Day 344 and the difference between death/PD and last adequate assessment[2] is more than 182 days Note: The scheduled assessments are every 8 weeks up to 6 months, then every 12 weeks The scheduled assessments windows are: ±7d;	

[1] The earliest of (i) Date of radiological assessment showing new lesion (if progression is based on new lesion); or (ii) Date of radiological assessment showing unequivocal progression in non-target lesions, or (iii) Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)

[2] An adequate assessment is defined as an assessment where the Investigator determined response is CR, PR, or SD. Note it can be scheduled or unscheduled.

[3] If PD and New anti-cancer therapy occur on the same day assume the progression was documented first e.g., outcome is progression and the date is the date of the assessment of progression)

7.2.3. Population of Interest

The secondary efficacy analyses will be based on the Modified All Treated population, unless otherwise specified.

7.2.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints/variables defined in Section 7.2.1 will be summarised using descriptive statistics, graphically presented (if appropriate), and listed.

Secondary Statistical Analyses
Endpoint(s)
DCR ORR CTC CRR PSA Week 4 RR
Method of Analysis
Exact two-sided 95% CI
Endpoint(s)
Duration of PSA Response Time to Disease Progression rPFS
Method of Analysis
Kaplan-Meier method (if data warrant) with first, second and third quartiles 95% CI based on a g-transformed confidence interval for S(t) where g is linear (Klein and Moeschberger method).

8. SAFETY ANALYSES

The safety analyses will be based on the All Treated population, unless otherwise specified. All analyses will be presented by dose level for each arm separately. A subgroup analysis by number of lines of prior therapy (L2 vs. Lx) may also be provided.

8.1. Adverse Events (AE) Analyses

AE analyses including the analysis of adverse events, SAEs and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 10: List of Data Displays.

All AEs will be graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. Adverse events will be coded by the Medical Dictionary for Regulatory Activities (MedDRA) to System Organ Class (SOC) and Preferred Term (PT).

An overview summary will be presented for AEs, including counts and percentages of subjects for the following

- Any AE,
- Non-serious AEs,
- AEs related to any study treatment,
- AEs related to GSK525762,
- AEs of Grade 3-4,
- Grade 3-4 AEs related to any treatment,
- Grade 3-4 AEs related to GSK525762,
- AEs leading to permanent discontinuation of any study treatment,
- AEs leading to permanent discontinuation of GSK525762,
- AEs leading to dose reductions of any study treatment,
- AEs leading to dose reductions of GSK525762,
- AEs leading to dose interruptions/delays of any study treatment,
- AEs leading to dose interruptions/delays of GSK525762,
- SAEs,
- SAEs related to any study treatment,
- SAEs related to GSK525762,
- Dose Limiting Toxicities.

A summary of non-serious AEs that occurred in strictly 5% of the subjects or above will be provided (no rounding for the percentage will be used in terms of 5% threshold, e.g. events with 4.9% incidence rate should not be included in this table). This summary will contain the number and percentage of subjects and the number of occurrences of common non-serious adverse events. The summary tables will be displayed by SOC and PT.

A summary of number and percentage of subjects with any adverse events by maximum grade will be produced. At the subject level a conservative approach will be used in computing the maximum grade when grades are missing, for instance when a grade will be

missing for at least one AE this subject maximum grade will be counted as unknown. AEs will be sorted by PT in descending order of total incidence. The summary will use the following algorithms for counting the subject:

- **PT row**: Subjects experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.
- **Any event row**: Each subject with at least one adverse event will be counted only once at the maximum grade no matter how many events they have.

In addition, the frequency and percentage of Adverse Events (AEs) (all grades) will be summarised and displayed in two ways: 1) in descending order of total incidence by PT only and 2) in descending order of total incidence by SOC and PT. In the SOC row, the number of subjects with multiple events under the same system organ class will be counted once.

Separate summaries will be provided for study treatment-related AEs, one for any treatment-related and one for GSK525762-related. A study treatment related AE is defined as an AE for which the investigator classifies the relationship to study treatment as "Yes". A worst-case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study treatment as 'Yes' or missing. The summary table will be displayed in descending order of total incidence by PT only. Summary of study treatment related AEs by maximum grade will also be provided.

All AEs will be listed. Additionally, a listing of subject IDs for each individual Treatment Emergent Adverse Events will be produced. Lastly a summary of the number of patients experiencing DLT's in each dose level will be provided.

8.2. Adverse Events of Special Interest Analyses

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of AE of special interest (AESI). These AESI are not defined in the protocol but are noted in the IB. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional AESIs, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of the database lock. The details of the planned displays are provided in Appendix 10: List of Data Displays.

The events of special interest include but are not limited to the following categories:

- Haematopoietic thrombocytopenia Standardized MedDRA Query (SMQ)
- Haemorrhages [excl laboratory terms] [NARROW] SMQ
- Anaemias nonhaemolytic and marrow depression High Level Group Term (HLGT)
- Torsade de pointes/QT prolongation [NARROW] SMQ
- Drug related hepatic disorders - comprehensive search [NARROW] SMQ
- Renal Prefered terms

Preferred terms for the events of special interest will be provided by the molibresib Pharma Safety representative before DBR based on the most up to date MedDRA version.

The number and percentage of subjects with these events will be summarised by categories of AESI, PT, and maximum toxicity grade in one table. The summary and listing of event characteristics for each category of AESI will also be provided, including number of subjects with any event, number of events, number of subjects with any event that is serious, number of subjects with any event that is related to study treatment, the outcome of the event, maximum grade and the action taken for the event. The percentage for the number of subjects with an event will be calculated with total number of subjects as the denominator. The percentage for the event characteristics will be calculated with number of subjects with event as the denominator. The worst-case approach will be applied at subject level for the event outcome and maximum grade (i.e., a subject will only be counted once as the worst-case from all the events experienced by the subject). For action taken to an event, subjects will be counted once per action (e.g., if a subject has an event leading to both study treatment discontinuation and dose reduction, the subject will be counted once under both actions).

For each category of AESI, a summary of onset and duration will be provided (Time to onset (days) and duration of first occurrence (days)). In addition to descriptive statistics (mean, median, minimum, maximum), time to onset will be summarised in categories of 1 to 14 days, 15 to 28 days, and >28 days, and duration of first occurrence will be summarised in categories of 1 to 5 days, 6 to 10 days, and >10 days.

8.3. Deaths and Serious Adverse Events

In the event that a subject has withdrawn consent, no data after the withdrawal of consent date from this subject including death is supposed to appear in the database, which should be part of the data cleaning process. All deaths will be summarised based on the number and percentage of subjects. This summary will classify subjects by time of death relative to the last dose of medication (>30 days or <=30 days) and the primary cause of death (disease under study, SAE related to study treatment, or other). A supportive listing will be generated to provide subject-specific details on subjects who died.

All SAEs will be tabulated based on the number and percentage of subjects who experienced the event. Separate summaries will also be provided for study treatment-related SAEs. The frequency and percentage of SAEs will be summarised in descending order of total incidence by PT only.

A study treatment-related SAE is defined as an SAE for which the investigator classifies the relationship to study treatment as “Yes”. A worst-case scenario approach will be taken to handle missing data, i.e. the summary table will include events with the relationship to study treatment as ‘Yes’ or missing.

SAEs are included in the listing of all AEs and separate supportive listings with subject-level details will be generated for both fatal and non-fatal SAEs.

8.4. Adverse Events Leading to Discontinuation of Study Treatment and Other Significant Adverse Events

The following categories of AEs will be summarised separately in descending order of total incidence by PT only and separate supportive listings will be generated with subject level details for those subjects:

- AEs Leading to Permanent Discontinuation of GSK525762
- AEs Leading to Dose Interruptions/Delays of GSK525762
- AEs Leading to Dose Reductions of GSK525762
- AEs Leading to Permanent Discontinuation of Any Study Treatment
- AEs Leading to Dose Interruptions/Delays of Any Study Treatment
- AEs Leading to Dose Reductions of Any Study Treatment

8.5. Extent of Exposure

Extent of exposure to GSK525762, abiraterone, and enzalutamide will be summarised separately.

The duration of exposure to study treatment in months (from first day to last day of treatment) will be summarised. Descriptive statistics including mean, median, standard deviation, minimum, and maximum will be calculated for time on study treatment. The duration of treatment will also be summarised based on the following categories: <3 months, 3-<6 month, 6-<12 months, >=12 months.

The subject's average daily dose, defined as the cumulative dose divided by the duration of exposure for each subject, will be summarised.

Dose reductions will be summarised by number of reductions and reasons for reductions. Dose interruptions/delays will be summarised by number of interruptions, reasons for interruptions and duration of interruption (days). The mean, standard deviation, median, minimum and maximum will be computed for the duration of interruptions as well as the number and percentage of the interruptions for <7, 7-14, >14 days. Summary of dose escalation will also be provided, if applicable. All the dose reductions, dose escalations and dose interruptions/delays will be listed separately.

Lastly, several summaries of study treatment exposure and dose modifications (e.g., summaries of total exposure, dose reductions, dose interruptions/delays, dose escalations, missed doses, and dose-limiting toxicities experienced) will be provided for GSK525762, abiraterone and enzalutamide. Corresponding listings will also be provided, including planned versus actual treatments received, drug accountability, total exposure, missed doses, and the various dose modifications (reductions, interruptions, delays, and escalations).

8.6. Clinical Laboratory Analyses

Laboratory evaluations including clinical chemistry, haematology, urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 10: List of Data Displays.

The assessment of laboratory toxicities will examine the following laboratory tests:

Clinical Chemistry
Sodium
Fasting Glucose
Potassium
Magnesium
Chloride
Calcium (total and ionized)
Total Carbon Dioxide
Total Protein
Blood Urea Nitrogen
Albumin
Creatinine
Lactate dehydrogenase
Haematology
White Blood cell count
Haemoglobin
Platelet count
Automated White Blood Cell Differential:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils
Liver Function
Bilirubin (Total and Direct)
Aspartate Aminotransferase
Alanine Aminotransferase
Alkaline Phosphatase
Urinalysis
Specific gravity
pH
Glucose
Protein
Blood
Ketones
Microscopic examination (if urinalysis is abnormal)
Cardiac
Troponin
NT-proBNP (N-terminal pro b-type natriuretic peptide)
Fasting Lipid Panel (Total Cholesterol, LDL, HDL, Triglycerides)

Other
Coagulation:
Prothrombin Time/INR
Partial Thromboplastin Time
Fibrinogen
Factor VII Assay
Endocrine:
Thyroid Stimulating Hormone (TSH)
Free Thyroxine 3 (Free T3)
Free Thyroxine 4 (Free T4)
Haemoglobin A1c
PSA
Testosterone
Safety Screening:
HIV
HbSag
HCV antibody
Pancreatic Markers:
Amylase
Lipase

A summary of laboratory values and change from baseline in lab values by scheduled visits using mean, median, standard deviation, minimum and maximum will be provided. Summaries of lab data will also be provided by maximum toxicity grade, using reported grades based on NCI-CTCAE v4.0.

Summaries of worst-case grade increase from baseline grade will be provided for all the lab tests that are gradable by NCI-CTCAE v4.0. These summaries will display the number and percentage of subjects with a maximum post-baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarised along with any increase to a maximum grade of 3 and any increase to a maximum grade of 4.

Missing baseline grade will be assumed as grade 0. In addition, the summary will include grade increase from baseline by scheduled visits. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarised as hyponatremia and hypernatremia.

For lab tests that are not gradable by NCI-CTCAE v4.0, summaries of worst-case changes from baseline with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarised at each scheduled visit as well as for the worst-case post-baseline results. If a subject has a decrease to low and an increase to high during the same time interval, then the subject is counted in both the “Decrease to Low” categories and the “Increase to High” categories. In addition, the summary will include worst-case changes from baseline with respect to normal range by scheduled visits.

Separate summary tables for haematology, chemistry, liver function, urinalysis, cardiac function, coagulation, endocrine, and pancreatic laboratory tests will be produced.

A supporting listing of laboratory data for subjects with abnormalities of potential clinical concern will be provided, as will a separate listing of laboratory data with character values.

Detailed derivation of baseline assessment is specified in Section 5.3.

Unless otherwise specified, the denominator used for computing percentages will be based on the number of subjects with non-missing values for the given scheduled visit.

Dipstick test results will be summarised at each scheduled visit. A supporting listing with subject level details will be provided.

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.

8.6.1. Analyses of Liver Function Tests

Summaries and listing of hepatobiliary laboratory events including possible Hy's law cases will be provided in addition to bilirubin (total and direct), AST, ALT, and alkaline phosphatase (ALP) as described above.

Possible Hy's law cases are defined as any elevated (ALT≥3×ULN and total bilirubin≥2×ULN (> 35% direct bilirubin)) or (ALT≥3xULN and INR>1.5, if INR measured). Total bilirubin≥2×ULN can be within 28 days following the ALT elevation and if direct bilirubin is available on the same day, it must be ≥ 35% of total bilirubin.

8.7. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs, ECHO/MUGA, performance status and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 10: List of Data Displays.

8.7.1. Vital Signs

Values of vital signs as well as the change from baseline will be summarised by scheduled visit using mean, median, standard deviation, minimum and maximum.

In addition, vital sign values will be categorized as follows:

- Systolic Blood Pressure (BP, mmHg): Grade 0 (≤120), Grade 1 (>120-<140), Grade 2 (≥140-<160) and Grade 3 (≥160)
- Diastolic BP (mmHg): Grade 0 (≤80), Grade 1 (>80-<90), Grade 2 (≥90-<100), and Grade 3 (≥100)
- Heart rate (beats/min): <60, ≥60-≤100, and >100

- Respiratory rate (breaths/min): <12, >12-≤18, >18-≤25, and >25
- Temperature (°C): ≤35, >35-<38, ≥38

Summaries of increase in vital signs from the baseline with respect to the categories defined above will be performed.

8.7.2. Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status will be summarised at baseline and each post-baseline scheduled visit. Summaries will use frequency and percentage of subjects at each planned assessment time. A summary of change from baseline by scheduled visits will be performed, as well as the worst-case post-baseline and the best-case post-baseline changes during the study (improved, no change, deteriorated).

8.7.3. ECG

Per protocol, triplicate 12-lead ECGs will be obtained, prior to dosing, during the study using a standard 12-lead ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QTcF intervals. Baseline QTcF value is determined by the mean of the triplicate Week1 Day1 pre-dose QTcF results (see Section 5.3). If these results are not available, then the mean QTcF of the screening triplicate ECG results will be used.A summary of the number and percentage of subjects who had normal and abnormal (clinically significant and not clinically significant) ECG findings will be displayed by scheduled visits as well as for the worst-case post-baseline.

Change from baseline in ECG values will be summarized at each scheduled assessment time and for the worst-case post-baseline. Only the post-baseline assessments that used the same source (i.e. local or central cardiologist read) as the baseline assessments will be used to derive the change from baseline, data from the two sources will not be combined.

QTcF prolongation will be monitored throughout the study. The QTc values based on Fridericia formula will be rounded to the integer and the values will be categorized into the following ranges: Grade 0 (<450 msec), Grade 1 (≥450-≤480 msec), Grade 2 (≥481-≤500 msec), and Grade 3 (≥501 msec).

Summaries of grade increase will be provided. These summaries will display the number and percentage of subjects with any grade increase, increase to grade 2 and increase to grade 3 at each scheduled assessment time and in the worst-case post-baseline. Missing baseline grade will be assumed as grade 0.

The changes in QTc values will be categorized into the clinical concern ranges which are specific to changes in QTc: ≥31-≤60 and >60 msec. A summary of change in QTc value will display the number and percentage of subjects with a change within each range at each scheduled assessment time and in the worst-case post-baseline. Subjects with missing baseline values will be excluded from this summary.

Listings of abnormal ECG findings and a listing of ECG values will be provided.

8.7.4. LVEF

Absolute change from baseline in LVEF will be summarised at each scheduled assessment time and in the worst-case post-baseline. Only the post-baseline assessments that used the same method (i.e. Electrocardiogram ECHO or Multiple Grated Acquisition MUGA) or source (i.e. local or central read)as the baseline assessments will be used to derive the change from baseline, data from different methods and sources should not be combined. The change from baseline will be categorized as follows:

- No change or any Increase (i.e. increase of - <10%, 10 - <20%, ≥20%)
- Any decrease (i.e. decrease of >0 - <10%, 10 - <20%, ≥20%)
- ≥10% decrease and ≥ LLN
- ≥10% decrease and < LLN
- ≥20% decrease and ≥ LLN
- ≥20% decrease and < LLN

LVEF results will also be listed with subject level details including absolute change from baseline.

8.7.5. Liver Events

For any liver events that occur during the study, the liver event information for RUCAM (Roussel Uclaf Causality Assessment Method) score will be summarised, including whether the subject was age 55 or over, liver imaging normal or not, a biopsy was taken or not, whether there was fasting or significant dietary change, whether the subject took any unconventional medications, timing when the event occurs (while on treatment or after stopping treatment) and summary statistics for time from first dose to start of liver event and time from last dose to start of liver event. If the number of events does not support a summary, then only listings will be produced.

For subjects with multiple events, the first event will be used for the summary tables. All events with subject level details will be displayed in a supporting listing.

9. PHARMACOKINETIC ANALYSES

9.1. Pharmacokinetic Analyses

9.1.1. Endpoint / Variables

9.1.1.1. Drug Concentration Measures

Two major metabolites of GSK525762, GSK3529246 and GSK3536835, have been observed in humans. GSK3536835 was found to be unstable under bioanalytical conditions. Therefore, the two major active metabolites were measured together following full conversion of GSK3536835 to GSK3529246 prior to analysis and the active metabolites (GSK3529246 + GSK3536835) are reported as one entity, GSK3529246.

Concentration of GSK525762, active metabolites (GSK3529246) and GSK525762 total active moiety (i.e. GSK525762 + GSK3529246 after conversion to nM concentrations) as well as abiraterone and enzalutamide will be listed for each subject.

Summaries of plasma concentration will be produced separately for GSK525762 in both ng/mL and nM, active metabolites (GSK3529246) in both ng/mL and nM and the total active moiety of GSK525762 (GSK525762 + GSK3529246 after conversion to nM concentrations) in nM. Plasma concentration-time data will be summarized using descriptive statistics (n, mean, SD, median, minimum and maximum) by planned relative assessment time.

One plot of concentration over time will be provided using actual elapsed time for Week 1, Week 3 and overall duration of study for GSK525762 (in nM), GSK3529246 (in nM), Total active moiety (in nM) and abiraterone.

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 13.5.3 Reporting Standards for Pharmacokinetic) for details of displays.

9.1.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of Phoenix. This will be the responsibility of the PK group at PAREXEL under the direction of Clinical Pharmacology Modeling and Simulation (CPMS) Department, GSK. All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed below will be determined from the concentration-time data for GSK525762, active metabolites (GSK3529246)), the total active moiety (i.e. GSK525762 + GSK3529246 after conversion to nM concentrations) and abiraterone/enzalutamide, as data permits.

The molecular weight of GSK525762 is 424 g/mol and the molecular weight of GSK3529246 is 396 g/mol.

The total active moiety concentration in nmol/L will be computed as (GSK525762 concentration in ng/mL / molecular weight of 424 * 1000) + (GSK3529246 concentration in ng/mL / molecular weight of 396 * 1000).

Pharmacokinetic parameters described in Table 3 will be determined from the plasma concentration-time data, as data permits.

Table 3 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
AUC (0-τ)	Area under the concentration-time curve over a dosing interval will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
Tmax	Time to reach Cmax, determined directly from the concentration-time data.
Trough concentration (C_τ)	Pre-dose (trough) concentration at the end of a dosing interval.

NOTES: Additional parameters may be included as required.

9.1.2. Summary Measure

Summaries of plasma concentration and pharmacokinetic parameters will be produced separately for GSK525762, active metabolites (GSK3529246) , the total active moiety of GSK525762, abiraterone and enzalutamide.

Plasma concentration-time data will be summarised using descriptive statistics (n, mean, SD, median, minimum and maximum) by planned relative assessment time. Mean and/ or median values will be plotted over time using nominal visit.

Concentration-time profiles for GSK525762, GSK3529246 and total active moiety will be overlaid on the same plot after conversion to nM concentrations.

The PK parameters described in Section 9.1.1.2 will also be summarised descriptively for plasma pharmacokinetic parameters (mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation, (Coefficient of Variation) CV% and 95% CI of log-transformed parameters (if applicable) will be reported.

9.1.3. Population of Interest

The pharmacokinetic analyses will be based on the Pharmacokinetic population, unless otherwise specified.

10. PHARMACODYNAMIC ANALYSIS

Tumour 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.

The pharmacodynamic analyses will be detailed in a Pharmacodynamic RAP supplement and will not be discussed as part of this RAP.

11. OTHER STATISTICAL ANALYSES

11.1. Value Evidence and Outcomes

The value evidence and outcomes analyses will be based on the Modified All Treated Subjects population, unless otherwise specified. All summaries and data listings will use treatment labels as specified in Section 5.1. Scoring details for EORTC-QLQ-C30, EORTC-QLQ-PR25, BPI-SF and PRO-CTCAE can be found in Appendix 6 Section 13.6.6. Details of data displays are presented in Appendix 10: List of Data Displays.

Summaries of absolute values and change from baseline of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC-QLQ-C30) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Prostate (EORTC-QLQ-PR25) scales will be provided in tables. Summaries of absolute values and change from baseline of the Brief Pain Inventory (BPI-SF) scores will be provided in tables. Summaries of absolute values and change from baseline of the PRO-CTCAE will be provided in tables. Single items EORTC-QLQ-C30, EORTC-QLQ-PR25, BPI-SF and PRO-CTCAE will be provided in listings.

Baseline will be defined as the visit prior to start of Week 1 Day 1 dosing.

11.1.1. EORTC-QLQ-C30

The EORTC-QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / Quality of Life (QoL) scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems.

11.1.2. EORTC-QLQ-PR25

While the EORTC-QLQ-C30 is an important tool for assessing the generic aspects of QoL, it has limitations and therefore a modular approach was adopted for disease-specific treatment measurements. An essential aspect of the “modular” approach to QoL assessment adopted by the EORTC Quality of Life Group is the development of modules specific to tumour site, treatment modality, or a QoL dimension, to be administered in addition to the core questionnaire (EORTC-QLQ-C30). The modules, like the core questionnaire, are designed for use in cancer clinical trials. The EORTC-QLQ-PR25 is a 25-item prostate cancer-specific scale intended to supplement, the EORTC-QLQ-30. It includes subscales assessing urinary symptoms (9 items), bowel symptoms (4 items), treatment-related symptoms (6 items) and sexual functioning (6 items). There are six prostate-specific domains: Urinary, Bowel, Use of Incontinence Aids, Treatment-Related Symptoms, Sexual Active and Sexual Function. Item scores are summed and transformed to a 0-100 scale; higher scores represent higher functioning for the two sexual domains but,

conversely, higher scores represent more symptoms (i.e. worse Health Related Quality of Life (HRQoL) for the symptom scales.

11.1.3. BPI-SF

The BPI-SF is a 9-item self-administered questionnaire. It uses simple numeric rating scales from 0 to 10 and gives two main scores: a pain intensity score and a pain interference score. The two scores are calculated Pain intensity score and Pain interference score: is calculated from items CCI to CCI and is used to rate the degree that pain interferes with CCI and CCI. The seven sub-items are rated from 0 CCI, to 10 CCI. The average of BPI-SF pain interference will be calculated at each routine visit as the mean of the scores for the 7 sub-items of pain interference.

BPI-SF item "pain at its worst in 24 hours" will be used to categorize patients into severity categories of 1-4 (mild), 5-6 (moderate) and 7-10 (severe). Proportions over time will be presented in stacked bar charts over time.

11.1.4. PRO-CTCAE

The PRO-CTCAE is a patient-reported outcome (PRO) measurement system developed to evaluate symptomatic toxicity in patients on cancer clinical trials. It was designed to be used as a companion to the Common Terminology Criteria for Adverse Events (CTCAE) The PRO-CTCAE Item Library includes 124 items representing 78 symptomatic toxicities drawn from the CTCAE. PRO-CTCAE items evaluate the symptom attributes of frequency, severity, interference, amount, presence/absence. Each symptomatic AE is assessed by 1-3 attributes. PRO-CTCAE responses are scored from 0 to 4 (or CCI CCI). There are as yet no standardized scoring rules for how to combine attributes into a single score or how best to analyze PRO-CTCAE data longitudinally. Scores for each attribute (frequency, severity and/or interference) will be presented descriptively (e.g. summary statistics or graphical presentations).

12. REFERENCES

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13. APPENDICES

13.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Specification document.

13.1.1. Exclusions from Per Protocol Population

No per protocol population is defined and used for this study.

13.2. Appendix 2: Schedule of Activities

13.2.1. Protocol Defined Schedule of Events

Refer to protocol Section 7.1 Time and Events Table.

13.3. Appendix 3: Assessment Windows

13.3.1. Definitions of Assessment Windows for Analyses

For PSA response at 12 weeks and PSA response confirmation at 4 weeks, 5 days assessment window will be applied.

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
Efficacy	PSA Response	W12	-5 days	+5 days	Week 12
	PSA Response Confirmation	W12 + 4 weeks	-5 days	+5 days	Week 16
	PSA Response	W4	-7 days	+7 days	Week 4
	DCR	24 weeks	163 days		Week 24

NOTES: DCR is defined as the percentage of subjects with confirmed PR or CR or a SD at 24 weeks (minimum 163 days to account for visit window). 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

13.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

13.4.1. Study Phases

Disease assessments and AEs, SAEs, death, laboratory data, vital signs. ECGs, echocardiograms, performance status results and other safety domains will be assigned to the treatment phases defined below. Partial dates will be imputed into full dates, if applicable, for slotting data to the appropriate categories below. Flag variables (time in relation to study treatment) indicating the study time periods will be added to these datasets.

Assessments and events will be classified according to the time of occurrence relative to Study Treatment Start Date.

Treatment Phase	Definition
Pre-Treatment	Date < Study Treatment Start Date
On-Treatment	Study Treatment Start Date ≤ Date ≤ Study Treatment Stop Date
abiraterone Run-In Period	Day -7 to Day 0
enzalutamide Run-in Period	Day –28 to Day 0 or Day -14 to Day 0
Onset Time Since 1st Dose (Days)	• If Treatment Start Date > AE Onset Date = AE Onset Date - Treatment Start Date • If Treatment Start Date ≤ AE Onset Date = AE Onset Date - Treatment Start Date +1 • Missing otherwise.
Duration (Days)	AE Resolution Date – AE Onset Date + 1

13.4.2. Treatment States

Assessments and events will be classified according to time of occurrence relative to the start and/or stop date of the study treatment.

13.4.2.1. Treatment States for Disease Response Data

Treatment State	Definition
Time to Progression	Date of Progression or Date of Last Disease Assessment - Study Treatment Start Date + 1
Time to Response	Date of First Partial or Complete Response of a Confirmed Partial or Complete Response – Study Treatment Start Date + 1
Duration of Response	Date of Progression – Date of First Partial or Complete Response of a Confirmed Partial or Complete Response + 1

13.4.3. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	If AE onset date is on or after treatment start date and on or before 30 days after treatment end date. • Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment End Date + 30 days. If AE onset date is prior to treatment start date and toxicity grade changes to worsening on or after treatment start date and on or before treatment end date + 30 days. • AE onset Date < Study Treatment Start date and Study Treatment Start Date ≤ AE Worsening Date ≤ Study Treatment End Date + 30 day.
Drug-related	If relationship is marked 'YES' on [Inform/CRF OR value is missing].

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment as long as it started after treatment.
- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

13.5. Appendix 5: Data Display Standards & Handling Conventions

13.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: US1SALX00259
HARP Compound	: GSK525762\mid204697
Analysis Datasets	
Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 & ADaM IG Version 1.1).	
Generation of RTF Files	
RTF files will be generated for SAC and IA upon request.	

13.5.2. Reporting Standards

General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx): o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics • Do not include subject level listings in the main body of the GSK Clinical Study Report. All subject level listings should be located in the modular appendices as ICH or non-ICH listings
Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DPs) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DPs.
Planned and Actual Time
• Reporting for tables, figures and formal statistical analyses: o Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. o The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate. • Reporting for Data Listings: o Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). o Unscheduled or unplanned readings will be presented within the subject's listings.
Unscheduled Visits
• Unscheduled visits will not be included in summary tables, except in cases where worst-case post-baseline is calculated. • Unscheduled visits will not be included in figures, unless otherwise specified.

• All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

13.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non-compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to SOP_00000314000: Non-compartmental Analysis of Clinical Pharmacokinetic Data. **Note**: Concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. **Note**: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarised graphical displays only. Assign zero to NQ values.
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by PK analyst	The following PK parameters will be derived by the PK Analyst: AUC0-τ, Cmax, Tmax and Cτ
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to Standards for Handling NQ Impacted PK Parameters.

13.6. Appendix 6: Derived and Transformed Data

13.6.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If multiple assessments on different days are reported for the same scheduled assessment, then the worst-case assessment for that scheduled assessment will be analysed. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day
• Calculated as the number of days from Study Treatment Start Date: ○ Ref Date = Missing → Study Day = Missing ○ Ref Date < Study Treatment Start Date → Study Day = Ref Date – Study Treatment Start Date ○ Ref Data ≥ Study Treatment Start Date → Study Day = Ref Date – (Study Treatment Start Date) + 1
Change from Baseline
• Change from Baseline = Post-Baseline Visit Value – Baseline • % Change from Baseline= 100 x (Post-Baseline Visit Value – Baseline) / Baseline If either the Baseline or Post-Baseline Visit Value is missing, Change from Baseline and % Change from Baseline is set to missing
Date of Response
For post-baseline disease assessments, the date of response (PR or better) is assigned to the earliest date of disease assessments; for other response categories (SD [or Non-CR/Non-PD], NE (Not Evaluable), PD), the date of response is assigned to the earliest date of disease assessments.
Date of New Anti-Cancer Therapy
Derived as the earliest date of new anti-cancer therapy, radiotherapy (where applicable) or cancer-related surgical procedure (where applicable). Missing or partial dates will be imputed for derivation of new anti-cancer therapy following rules specified in Section 13.7.2.1

13.6.2. Study Population

Demographics
Age
• GSK standard Integrated Data Standards Library (IDSL) algorithms will be used for calculating age where birth date will be imputed as follows: o Any subject with a missing day will have this imputed as day '15'. o Any subject with a missing date and month will have this imputed as '30th June'. o Birth date will be presented in listings as 'YYYY'.
Body Mass Index (BMI)
Calculated as Weight (kg) / [Height (m)]^2
Change from Baseline
Change from Baseline = Post-Baseline Visit Value – Baseline % Change from Baseline= 100 x (Post-Baseline Visit Value – Baseline) / Baseline If either the Baseline or Post-Baseline Visit Value is missing, Change from Baseline and % Change from Baseline is set to missing
Date of Response
For post-baseline disease assessments, the date of response (PR or better) is assigned to the earliest date of disease assessments; for other response categories (SD [or Non-CR/Non-PD], NE, PD), the date of response is assigned to the earliest date of disease assessments.
Date of New Anti-Cancer Therapy
Derived as the earliest date of new anti-cancer therapy, radiotherapy (where applicable) or cancer-related surgical procedure (where applicable). Missing or partial dates will be imputed for derivation of new anti-cancer therapy following rules specified in Section 13.7.2.1.

13.6.3. Efficacy

Primary Endpoint
PSA Response Rate (RR)
• Defined as proportion of subjects with a decrease of ≥ 50% in the PSA concentration from the baseline PSA value determined at least 12 weeks (±5 days) after start of treatment and confirmed ≥ 4 weeks later by an additional PSA evaluation.
Disease Control Rate (DCR)
• DCR is defined as the percentage of subjects with confirmed PR or CR or a SD at 24 weeks (minimum 163 days to account for visit window). 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
• Duration of PSA response is calculated from the time the PSA value first declines by at least 50% from 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 2ng/mL from the nadir . 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

Primary Endpoint
Time to disease progression
• Time to disease progression is defined as the time from first dose date of study treatment to disease progression defined as one or more of the following criteria: o Radiographic progression by PCWG3-modified RECIST 1.1 for subjects with measurable disease o Bone progression on bone scan according to the PCGW3 criteria o PSA progression according to the PCWG3 criteria accompanied by any one of the following: investigator-defined clinical progression or either of the above RECIST 1.1 or bone progression o Investigator-defined clinical progression o Death due to any cause.
Objective Response Rate
• The ORR rate is defined as the percentage of subjects with a confirmed CR or a PR at any time as per PCWG3-modified RECIST 1.1.
CTC Response Rate
• 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) for subjects with unfavourable CTC at baseline.
Composite Response Rate (CRR)
• CRR is a composite endpoint based on the following – o Response based on PCWG3 modified RECIST 1.1 o PSA decrease of ≥50% from baseline at Week 12 or thereafter o Or CTC count conversion from unfavourable (>=5/7.5mL) at baseline to favourable (<5/7.5mL) confirmed by a second assessment at least 4 weeks later.
PSA Week 4 Response Rate (Week 4 RR)
• 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.
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 1.1 or progression on bone scan.

13.6.4. Safety

Treatment Compliance
• Treatment compliance for GSK525762 will be calculated based on the formula: Treatment Compliance = Total Cumulative Actual Dose/ (Planned Treatment Duration in Days * Frequency)
Extent of Exposure
• Number of days of exposure to GSK525762/Abi/Enza will be calculated based on the formula: Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1 • Participants who were not screen failures but did not report a treatment start date will be categorised as having zero days of exposure. • The cumulative dose for GSK525762 will be based on the formula: Cumulative Dose = Sum of (Number of Days x Total Daily Dose)

• If there are any treatment breaks during the study, exposure data will be adjusted accordingly.
Adverse Events
AE'S OF Special Interest
• Haematopoietic thrombocytopenia SMQ • Haemorrhages [excl laboratory terms] [NARROW] SMQ • Anaemias nonhaemolytic and marrow depression HLGT • Torsade de pointes/QT prolongation [NARROW] SMQ • Drug related hepatic disorders - comprehensive search [NARROW] SMQ • Renal Prefered Terms

13.6.5. Pharmacokinetic

PK Parameters
GSK525762, GSK525762 relevant metabolites (i.e. GSK3529246) and GSK525762 total active moiety (i.e. GSK525762 + GSK3529246 after conversion to nM concentrations) as well as abiraterone and enzalutamide • If the concentrations are presented in ng/mL, then the conversion factor to nM is to multiply the concentration by (1000/MW).
• PK parameters to be derived: Cmax, AUC0-τ, Tmax and Cτ

13.6.6. Value Evidence and Outcomes

EORTC QLQ-C30 • The EORTC-QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale. • All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. ➢ Thus, a **high score for a functional scale** represents a high / healthy level of functioning, ➢ a **high score for the global health status / QoL** represents a high QoL, ➢ but a **high score for a symptom scale / item** represents a high level of symptomatology / problems. • The principle for scoring these scales is the same in all cases: ➢ Estimate the average of the items that contribute to the scale; this is the *raw score*. ➢ Use a linear transformation to standardise the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.
Technical Summary In practical terms, if items I_1, I_2, ... I_n are included in a scale, the procedure is as follows: **Raw score** Calculate the raw score RawScore = CCI [redacted] **Linear transformation**

EORTC QLQ-C30

Apply the linear transformation to 0-100 to obtain the score S,

- Functional scales: CCI [redacted]
- Symptom scales / items:and Global health status / QoL: CCI [redacted]

Range is defined as the difference between the maximum possible value of RS and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of RS equals the range of the item values. Most items are scored 1 to 4, giving range = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with range = 6, and the initial yes/no items on the earlier versions of the QLQ-C30 which have range = 1.

EORTC QLQ-C30

	Scale	Number of Items	Item Range	Item Numbers	Functional Scales
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.					

"Item range" is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving range= 3.

***Items for the scales marked * are scored positively (i.e. "CCI [redacted]" is best) and therefore use the same algebraic equation as for symptom scales; however, the Body Image scale uses the algebraic equation for functioning scales.**

EORTC-QLQ-PR25

- While the EORTC-QLQ-C30 is an important tool for assessing the generic aspects of QOL, it has limitations and therefore a modular approach was adopted for disease-specific treatment measurements. An essential aspect of the "modular" approach to QoL assessment adopted by the EORTC Quality of Life Group is the development of modules specific to tumour site, treatment modality, or a QoL dimension, to be administered in addition to the core questionnaire (EORTC-QLQ-C30). The modules, like the core questionnaire, are designed for use in cancer clinical trials.
- The EORTC-QLQ-PR25 is a 25-item prostate cancer-specific scale intended to supplement, the EORTC QLQ-30. It includes subscales assessing urinary symptoms (9 items), bowel symptoms (4 items), treatment-related symptoms (6 items) and sexual functioning (6 items). There are six prostate-specific domains: Urinary, Bowel, Use of Incontinence Aids, Treatment-Related

EORTC-QLQ-PR25

Symptoms, Sexual Active and Sexual Function. Item scores are summed and transformed to a 0-100 scale; higher scores represent higher functioning for the two sexual domains but, conversely, higher scores represent more symptoms (i.e. worse HRQoL) for the symptom scales. Items are 4-point Likert response options of 1 CCI to 4 CCI

- The principle for scoring these scales is the same in all cases:
  - Estimate the average of the items that contribute to the scale; this is the *raw score*.
  - Use a linear transformation to standardise the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

Technical Summary

In practical terms, if items I_1, I_2, ... I_n are included in a scale, the procedure is as follows:

Raw score
Calculate the raw score

RawScore = CCI

Linear transformation
Apply the linear transformation to 0-100 to obtain the score *S*,

- Functional scales: CCI
- Symptom scales / items: CCI

Range is the difference between the maximum possible value of RS and the minimum possible value. The EORTC-QLQ-PR25 has been designed so that all items in any scale take the same range of values. Therefore, the range of RS equals the range of the item values. Items are scored 1 to 4, giving range = 3.

EORTC QLQ-PR25

	Scale	Number of Items	Item Range	Item Numbers	Functional Scales
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.					

"Item range" is the difference between the possible maximum and the minimum response to individual items.

***Items for the scales marked * are scored positively (i.e. "CCI" is best) and therefore use the same algebraic equation as for symptom scales; however, the Body Image scale uses the algebraic equation for functioning scales.**

Core questionnaire: The EORTC-QLQ-C30 is a "core questionnaire" which incorporates a range of physical, emotional and social health issues relevant to a broad spectrum of cancer patients; the core questionnaire should be used, unmodified, in all QLQ assessments.

Items: The individual questions on the EORTC- QLQ-C30 are called items, and are described as Q1, Q2, Q3, etc., where the suffix corresponds to the question-number on the QLQ questionnaire.

Module: The core questionnaire may be supplemented by diagnosis-specific and/or treatment- specific questionnaire modules. Modules should be used unmodified and in conjunction with the core questionnaire.

Raw score: The score formed by averaging the items that are included in a particular function or symptom scale.

Scales: The QLQ comprises distinct scales, each of which represents a different aspect of QoL.

Scale score: The raw score transformed to a standardised 0 - 100 final "scale score".

Brief Pain Inventory Short Form (BPI-SF)

- The BPI-SF is a 9-item self-administered questionnaire. It uses simple numeric rating scales from 0 to 10 and gives two main scores: a pain intensity score and a pain interference score. The two scores are calculated as follows:
  - Pain intensity score is calculated from the four items (items CCI and CCI for CCI, CCI and CCI. Each item is rated from 0 CCI to 10 CCI CCI. The average of BPI-SF pain intensity will be calculated at each routine visit as the mean of the 4 scores for the 4 items of pain intensity.
  - Pain interference score is calculated from items CCI to CCI and is used to rate the degree that pain interferes with CCI CCI, and CCI. The seven sub-items are rated from 0 CCI, to 10 CCI The average of BPI-SF pain interference will be calculated at each routine visit as the mean of the scores for the 7 sub-items of pain interference.

Technical Summary

In practical terms, if items I_1, I_2, ... I_n are included in a scale, the procedure is as follows:

Score
Calculate the score as:

Score = CCI

BPI-SF

	Scale	Number of Items	Item Range	Item Numbers	Functional Scales
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.					

Brief Pain Inventory Short Form (BPI-SF)

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.	

"Range" is the difference between the possible maximum and the minimum response to individual items.

Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

- The response frequency distribution and proportion of subjects for each PRO-CTCAE item by visit will be presented and grouped first by visit, then by related term.
- For subjects who do not have a response due to skipping patterns, they should be reported as "Not applicable". Other subjects who do not provide a response or have dropped out would be treated as missing data. The number of subjects who provide a response should be reflected in the number of observations for the sample.
- In addition to reporting the number and percent of subjects who have selected each response category, assign a value (See coding table below: CCI for CCI ; CCI for CCI) and calculate the Mean (SD) and Median values for all subjects who have a valid response for a given visit. Subjects with missing or incomplete data (either due to drop outs, or subjects who have not provided a response – either due to missing data or skip patterns) should be excluded from calculating the Mean and Median.

	Levels and related code values
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.	

- PRO-CTCAE responses should also be summarized by changes in health state. For each subject compare their current response with the response from their prior assessment and determine whether their symptoms improved, worsened or were stable:
  - Improved = current response level < prior response level
  - Worsened = current response level > prior response level
  - Stable = current response level = prior response level
- Due to conditional branching and skip patterns it is possible that a response option may be missing, in these cases, the lowest level would be imputed in order to calculate the state change. Subjects who have data missing for other reasons (missing data, drop out) will be excluded for any item/visit where they have missing data.
- In addition to reporting the response frequencies by visit, as suggested by FDA, report the results of PRO-CTCAE alongside the corresponding clinician-graded CTCAE results.
- Categorize the highest level reported as either "Any Level" (subjects who had either a CTCAE or PRO-CTCAE response >0) or "High Level" (subjects who experienced ≥3 grade CTCAE or PRO-CTCAE response).
- Listings should include responses values (0-4, null for missing) for all PRO-CTCAE Items by subject by visit.

13.7. Appendix 7: Reporting Standards for Missing Data

13.7.1. Premature Withdrawals

Element	Reporting Detail
General	• All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

13.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Responder Analysis	For endpoints which determine the percentage of responders, subjects with unknown or missing response will be treated as non-responders and will be included in the denominator when calculating the percentages.

13.7.2.1. Handling of Missing and Partial Dates

Imputed partial dates can be used to derive study day, duration, or elapsed time variables unless otherwise specified. Imputed dates will not be used for deriving the last contact date in the overall survival analysis dataset.

With the exception of new anti-cancer start date on the Oncology time to event analysis dataset and exposure end date on the Exposure analysis dataset, imputed dates will also not be stored on datasets.

Imputed dates will not be displayed in listings. However, where necessary, display macros may impute dates as temporary variables for the purpose of sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study time periods or for specific analysis purposes as outlined below.

The partial date imputation will follow ADaM conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation.

The flag variable can contain the values: blank, 'D', 'M', 'Y'.

blank: indicates that no imputation was done

D='Day': indicates that the day portion of the date is imputed

M='Month': indicates that the month and day portions of the date are imputed

Y='Year': indicates that the entire date (year, month, and day) is imputed

Example of date variables:

XYZD_ – character date variable

XYZDT – numeric date variable

XYZDTFL – flag variable

Details on imputing partial dates for specific datasets are outlined below.

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 4: Study Phases and Treatment Emergent Adverse Events ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. If completely missing start dates, TEAE flag is Yes. • Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied.
Anti-Cancer Therapy and Radiotherapy	• Completely missing start or end dates will remain missing, with no imputation applied. • Partial start dates will be imputed using the following convention: ○ If both month and day are missing, no imputation will be applied ○ If only day is missing: ▪ If the month of partial date is the same as the month of last dosing date, minimum of (last dosing date + 1, last day of the month) will be used for the day. ▪ If the month of partial date is the same as the month of last disease assessment and the last disease assessment is PD, minimum of (last date of disease assessment + 1, last day of the month) will be used for the day. ▪ If both conditions above are met, the later date will be used for the day. ▪ Otherwise, a '01' will be used for the day. • No imputation for partial end dates will be performed.
Surgical Procedures	• Completely missing start or end dates will remain missing, with no imputation applied. • Partial start dates will be imputed using the following convention: ○ If both month and day are missing, no imputation will be applied ○ If only day is missing:

	▪ If the month of partial date is the same as the month of last dosing date, minimum of (last dosing date + 1, last day of the month) will be used for the day. ▪ If the month of partial date is the same as the month of last disease assessment and the last disease assessment is PD, minimum of (last date of disease assessment + 1, last day of the month) will be used for the day. ▪ If both conditions above are met, the later date will be used for the day. ▪ Otherwise, a '01' will be used for the day. • No imputation for partial end dates will be performed.
Concomitant Medications/Medical History/Blood Products	• Partial dates for any concomitant medications recorded in the eCRF will be imputed using the following convention: o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month o If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings. • No Imputation for completely missing start or end dates
Time to Event and Response for Anti-Cancer Therapy Where applicable: Radiotherapy, Surgical Procedures	• Start dates for subsequent anti-cancer therapy, radiotherapy (where applicable), and surgical procedures (where applicable) will be temporarily imputed in order to define event and censoring rules for progression-free survival, response rate, or duration of response (i.e. start date for new anti-cancer therapy). Dates will only be imputed when a month and year are available, but the day is missing. The imputed dates will not be stored on the anti-cancer therapy, radiotherapy, or surgical procedure datasets. The following rules will be used to impute the date when partial start dates are present on anti-cancer therapy radiotherapy, and/or surgical procedures datasets. • No Imputation for completely missing start dates • No imputation for missing start day and month (**note**: the eCRF should only allow for missing day) • If partial start date falls in the same month as the last dose of study treatment, then assign to earlier of (date of last dose of study treatment+1, last day of month). • If partial start date falls in the same month as the subject's last assessment and the subject's last assessment is progressive disease (PD), then assign to earlier of (date of PD+1, last day of month). • If both rules above apply, then assign to latest of the 2 dates • Otherwise, impute missing day to the first of the month. • No imputation for partial end dates will be performed
GSK525762/ abiraterone / enzalutamide Exposure End Dates for Subjects Who Are Still on Study at the Time of Analysis	• If treatment discontinuation date is missing, then assign exposure end date as the earliest of: o the date of the data cut-off, o the date of withdrawal from the study, or o the date of death. • The imputed exposure end date will be used to calculate cumulative dose and exposure duration.

	• The imputed exposure end date will be stored in the exposure analysis dataset and an exposure end date imputation flag variable will be derived indicating which exposure end date records are imputed. • Imputed exposure end dates will also be stored on the study treatment end date variable. • For subjects who are still on study treatment, the on-therapy indicator variables (time in relation to study treatment) are assigned to on-therapy for all records where the 'dataset' 'date' is after or on the study treatment start date

13.8. Appendix 8: Values of Potential Clinical Importance

13.8.1. Laboratory Values

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern. The laboratory reference ranges will be provided on the listings of laboratory data. Clinical laboratory test results outside of the reference range will be flagged in the listings.

To identify laboratory values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign grades to the relevant laboratory parameters. NCI-CTCAE v4.0 can be found at http://ctep.cancer.gov/reporting/ctc.html.

For laboratory data which are not listed in the NCI CTCAE v4.0, a summary of values outside the normal range will be provided.

13.8.2. ECG

Following table show the potential clinical importance criteria of 12-Lead ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTcF Interval	msec	≥ 450	< 481
		≥ 481	< 501
		≥ 501	
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75	> 110
Change from Baseline			
Decrease from baseline QTcF Interval	msec	> 30	≤ 60
		> 60	
Increase from Baseline QTcF	msec	>30	≤ 60
		> 60	

13.8.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	>120	<140 (Grade 1)
	mmHg	≥140	<160 (Grade 2)
	mmHg		≥160 (Grade 3)
Diastolic Blood Pressure	mmHg	> 80	< 90 (Grade 1)
	mmHg	≥ 90	< 100 (Grade 2)
	mmHg		≥ 100 (Grade 3)
Heart Rate	bpm	< 60	> 100
Temperature	Degrees C	≤ 35	≥ 38

13.8.4. Left Ventricular Ejection Fraction

To identify LVEF values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Ejection fraction decreased'.

LVEF	Units	Clinical Concern Range
Absolute Change from Baseline	%	0= < Increase < 10
	%	10 ≤ Increase < 20
	%	Increase ≥ 20
	%	0 < Decrease < 10
	%	10 ≤ Decrease < 20
	%	Decrease ≥ 20
	%	Decrease ≥ 0 and ≥ LLN
	%	Decrease ≥ 10 and < LLN
Relative Percent Change from Baseline	%	Decrease ≥ 20 and ≥ LLN
	%	Decrease ≥ 20 and < LLN

13.9. Appendix 9: Abbreviations & Trade Marks

13.9.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical
AUC(0-τ)	Area under the curve over a dosing interval
BID	Bis in die - Twice daily
BP	Blood Pressure
BPI	Brief Pain Inventory
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
Cmax	Maximum observed concentration
CPMS	Clinical Pharmacology Modelling & Simulation
CRPC	Castrate-resistant prostate cancer
CRR	Composite response rate
CR	Complete response
CNV	Copy number variation
CSMU	Clinically significant minimum utility
CSR	Clinical Study Report
Cτ	Pre-dose (trough) concentration at the end of a dosing interval
CTC	Circulating tumor cells
DBF	Database freeze
DBR	Database Release
DCR	Disease Control Rate
DDI	Drug-drug interactions
DL80	80 mg Dose Level
DL120	120 mg Dose Level
DLT	Dose-limiting toxicity
DP	Decimal Places
DS	Disposition dataset
dU	Utility of a given dose
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECHO	Echocardiogram
eCRF	Electronic Case Record Form
EC50	50% of the maximum effect
Emax	Maximum effect
EORTC – QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30
EORTC – QLQ-PR25	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-25
GSK	GlaxoSmithKline

IA	Interim Analysis
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
LLN	Lower limit of normal
LVEF	Left Ventricular Ejection Fraction
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MFD	Maximum feasible dose
mTPI	Modified toxicity probability interval
MTD	Maximum tolerated dose
NE	Not evaluable
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria
NGS	Next-generation sequencing
ORR	Overall response rate
OS	Overall survival
PCWG3	Prostate cancer working group 3
PD	Progressive Disease
PK	Pharmacokinetic
PR	Partial response
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%
PSMA	Prostate-specific membrane antigen
PT	Preferred term
QoL	Quality of life
QTcF	Friderica's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RECIST	Response Evaluation Criteria In Solid Tumours
RP2D	Recommended Phase II dose
rPFS	Radiological progression free survival
RR	Response rate
RNA	Ribonucleic acid
RS	Response dataset
SAE	Serious adverse event
SAC	Statistical Analysis Complete
SD	Stable disease
SDTM	Study Data Tabulation Model
SNV	Single-nucleotide variants
SOC	System Organ Class
SOP	Standard Operation Procedure
SRT	Safety review team
TA	Therapeutic Area
TFL	Tables, Figures & Listings
Tmax	Time to maximum concentration
TTG	Time to tumour growth
ULN	Upper limit of normal

13.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

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SAS

13.10. Appendix 10: List of Data Displays

13.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.23	
Efficacy	2.1 to 2.19	2.1 to 2.10
Safety	3.1 to 3.65	
Pharmacokinetic	4.1 to 4.13	4.1 to 4.4
Section	**Listings**	
ICH Listings	1 to 58	
Other Listings	59 to 80	

13.10.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 11: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln

NOTES: Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

13.10.3. Deliverables

Delivery	Description
DE	Dose Escalation
IA	Interim Analysis
SAC	Primary Statistical Analysis Complete

13.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	All Treated	ES1	Summary of Subject Status and Reason for Study Withdrawal	By Dose Level for each Arm Order Reasons for Study Withdrawal as displayed in the eCRF.	IA, SAC
1.2.	All Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	By Dose Level for each Arm	SAC
1.3.	All Treated	SD4	Summary of Treatment Status and Reasons for Discontinuation of GSK525762	By Dose Level for each Arm Order Reasons for Discontinuation as displayed in the eCRF	IA, SAC
1.4.	All Treated	SD4	Summary of Treatment Status and Reasons for Discontinuation of enzalutamide	By Dose Level for each Arm Order Reasons for Discontinuation as displayed in the eCRF	IA, SAC
1.5.	All Treated	SD4	Summary of Treatment Status and Reasons for Discontinuation of abiraterone	By Dose Level for each Arm Order Reasons for Discontinuation as displayed in the eCRF	SAC
Populations Analysed					
1.6.	All Screened	SP1	Summary of Study Population	By Dose Level for each Arm Add footnote with populations definition/criteria.	IA, SAC

Protocol Deviations					
1.7.	All Treated	DV1	Summary of Major Protocol Deviations	By Dose Level for each Arm	SAC
Demographic and Baseline Characteristics					
1.8.	All Treated	DM1	Summary of Demographic Characteristics	By Dose Level for each Arm	DE, IA, SAC
1.9.	All Treated	DM8	Summary of Race and Racial Combinations	By Dose Level for each Arm	SAC
1.10.	All Treated	DM11	Summary of Age Ranges	By Dose Level for each Arm	SAC
1.11.	All Treated	PS1A	Summary of Performance Status at Baseline	By Dose Level for each Arm Only include Baseline visit from Standard	SAC
1.12.	All Treated	LA1	Summary of Disease Burden at Baseline	By Dose Level for each Arm	SAC
1.13.	All Treated	DC1	Summary of Disease Characteristics at Initial Diagnosis	By Dose Level for each Arm Include in summary: stage at initial diagnosis, time since latest disease progression (in weeks), method by which progression was determined (radiological vs PSA rise) on prior disease progression	IA, SAC
1.14.	All Treated	DC2	Summary of Disease Characteristics at Screening	By Dose Level for each Arm	IA, SAC
Prior and Concomitant Medications					
1.15.	All Treated	MH1	Summary of Prior Medical Conditions	By Dose Level for each Arm	SAC
1.16.	All Treated	MH1	Summary of On Treatment Medical Conditions	By Dose Level for each Arm	SAC
1.17.	All Treated	OSP1	Summary of Prior Cancer-Related Surgical Procedures	By Dose Level for each Arm	SAC
1.18.	All Treated	OSP1	Summary of On Treatment Cancer Related Surgical Procedure	By Dose Level for each Arm	SAC
1.19.	All Treated	CM8	Summary of Concomitant Medication by Ingredient	By Dose Level for each Arm	SAC

				Medications to be sorted in descending order of overall incidence.	
Anti-Cancer Therapies					
1.20.	All Treated	AC1	Summary of Prior Anti-Cancer Therapy	By Dose Level for each Arm	IA, SAC
1.21.	All Treated	CM1	Summary of Prior Dictionary Coded Anti-Cancer Therapy	By Dose Level for each Arm	SAC
1.22.	All Treated	AC3	Summary of Number of Prior Anti-Cancer Therapy Regimens	By Dose Level for each Arm	SAC
1.23.	All Treated	AC4	Summary of Best Response to the Most Recent Prior Anti-Cancer Therapy	By Dose Level for each Arm	IA, SAC

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	All Treated	ES1	Summary of Subject Status and Reason for Study Withdrawal	By Dose Level for each Arm Order Reasons for Study Withdrawal as displayed in the eCRF.	IA, SAC
1.2.	All Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	By Dose Level for each Arm	SAC
1.3.	All Treated	SD4	Summary of Treatment Status and Reasons for Discontinuation of GSK525762	By Dose Level for each Arm Order Reasons for Discontinuation as displayed in the eCRF	IA, SAC
1.4.	All Treated	SD4	Summary of Treatment Status and Reasons for Discontinuation of enzalutamide	By Dose Level for each Arm Order Reasons for Discontinuation as displayed in the eCRF	IA, SAC
1.5.	All Treated	SD4	Summary of Treatment Status and Reasons for Discontinuation of abiraterone	By Dose Level for each Arm Order Reasons for Discontinuation as displayed in the eCRF	SAC
Populations Analysed					
1.6.	All Screened	SP1	Summary of Study Population	By Dose Level for each Arm Add footnote with populations definition/criteria.	IA, SAC

Protocol Deviations					
1.7.	All Treated	DV1	Summary of Major Protocol Deviations	By Dose Level for each Arm	SAC
Demographic and Baseline Characteristics					
1.8.	All Treated	DM1	Summary of Demographic Characteristics	By Dose Level for each Arm	DE, IA, SAC
1.9.	All Treated	DM8	Summary of Race and Racial Combinations	By Dose Level for each Arm	SAC
1.10.	All Treated	DM11	Summary of Age Ranges	By Dose Level for each Arm	SAC
1.11.	All Treated	PS1A	Summary of Performance Status at Baseline	By Dose Level for each Arm Only include Baseline visit from Standard	SAC
1.12.	All Treated	LA1	Summary of Disease Burden at Baseline	By Dose Level for each Arm	SAC
1.13.	All Treated	DC1	Summary of Disease Characteristics at Initial Diagnosis	By Dose Level for each Arm Include in summary: stage at initial diagnosis, time since latest disease progression (in weeks), method by which progression was determined (radiological vs PSA rise) on prior disease progression	IA, SAC
1.14.	All Treated	DC2	Summary of Disease Characteristics at Screening	By Dose Level for each Arm	IA, SAC
Prior and Concomitant Medications					
1.15.	All Treated	MH1	Summary of Prior Medical Conditions	By Dose Level for each Arm	SAC
1.16.	All Treated	MH1	Summary of On Treatment Medical Conditions	By Dose Level for each Arm	SAC
1.17.	All Treated	OSP1	Summary of Prior Cancer-Related Surgical Procedures	By Dose Level for each Arm	SAC
1.18.	All Treated	OSP1	Summary of On Treatment Cancer Related Surgical Procedure	By Dose Level for each Arm	SAC
1.19.	All Treated	CM8	Summary of Concomitant Medication by Ingredient	By Dose Level for each Arm	SAC

				Medications to be sorted in descending order of overall incidence.	
Anti-Cancer Therapies					
1.20.	All Treated	AC1	Summary of Prior Anti-Cancer Therapy	By Dose Level for each Arm	IA, SAC
1.21.	All Treated	CM1	Summary of Prior Dictionary Coded Anti-Cancer Therapy	By Dose Level for each Arm	SAC
1.22.	All Treated	AC3	Summary of Number of Prior Anti-Cancer Therapy Regimens	By Dose Level for each Arm	SAC
1.23.	All Treated	AC4	Summary of Best Response to the Most Recent Prior Anti-Cancer Therapy	By Dose Level for each Arm	IA, SAC

13.10.5. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PSA Response Rate					
2.1.	Modified All Treated	PSA_NS1	Summary of PSA Response determined >= 12 Weeks after Treatment (With Confirmation)	By Dose Level for each Arm. By L2 vs. Lx subgroups and total Add baseline PSA value.	IA, SAC
2.2.	Modified All Treated	PSA_NS1	Summary of PSA Response determined >= 12 Weeks after Treatment (With Confirmation) by Prior Treatment (Lx or L2)	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Add baseline PSA value.	IA, SAC
2.3.	Modified All Treated	PSA_NS1	Summary of PSA Response determined >= 12 Weeks after Treatment (With and Without Confirmation)	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	IA, SAC

				Add baseline PSA value.	
2.4.	Modified All Treated	PSA_NS1	Summary of PSA Response determined >= 12 Weeks after Treatment (With and Without Confirmation) by Prior Treatment (Lx or L2)	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Add baseline PSA value.	IA, SAC
Secondary Endpoints					
2.5.	Modified All Treated	RE1c	Summary of Investigator-Assessed Disease Control Rate with Confirmation (RECIST 1.1 Criteria)	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
2.6.	Modified All Treated	TTE6	Summary of Kaplan-Meier Estimates of Time to Progression	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
2.7.	Modified All Treated	RE1a	Summary of Best Overall Response (With Confirmation)	Include DCR. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	IA, SAC
2.8.	Modified All Treated	RE1a	Summary of Best Overall Response (With and Without Confirmation)	Include DCR. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	IA, SAC
2.9.	Modified All Treated	RE1a	Summary of Best Overall Response (With Confirmation) by prior treatment (Lx or L2)	Include DCR. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	IA, SAC
2.10.	Modified All Treated	RE1a	Summary of Best Overall Response (With and Without Confirmation) by prior treatment (Lx or L2)	Include DCR. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	IA, SAC

2.11.	Modified All Treated	RE1a	Summary of Investigator Assessed Best Response (With Confirmation)	Include DCR. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
2.12.	Modified All Treated	RE1a	Summary of Investigator Assessed Best Response (Without Confirmation)	Include DCR. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
2.13.	Modified All Treated	RE1a	Summary of CTC Response (Confirmed)	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Add footnote: "Subjects with CTC<5/7.5 mL at baseline will be excluded from this analysis"	SAC
2.14.	Modified All Treated	LB1	Summary of Percent Change from Baseline in CTC Actual Count by Visit	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
2.15.	Modified All Treated	RE1a	Summary of Composite Response Rate (CRR) (Confirmed)	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
2.16.	Modified All Treated	RE1a	Summary of Week 4 PSA Response Rate	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
2.17.	Modified All Treated	PSA_NS1	Summary of Week 4 PSA Response Rate – Confirmed	Include percentage of subjects having PSA ≥ 25% increase from baseline at 4 weeks. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC

2.18.	Modified All Treated	TTE6	Summary of Kaplan-Meier Estimates of Radiographic Progression-Free Survival (rPFS)	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
2.19.	Modified All Treated	PPUF_NS6	Summary of Posterior Probabilities for Utility Function.	By Arm. By L2 vs. Lx subgroups and total	IA

13.10.6. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.1.	Modified All Treated	RE8A	Waterfall Plot of Maximum Reduction from Baseline in PSA	The plot will be color-coded for best overall response with confirmation. Indication of the subject number and dose level will be provided below the plot. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
2.2.	Modified All Treated	SP_NS7	Spider Plot with Percent Change at Maximum Reduction from Baseline in PSA	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
2.3.	Modified All Treated	SP_NS7	Spider Plot of Percent Change from Baseline in PSA	Indication of the subject number and dose level will be provided below the plot. By Dose Level for each Arm.	IA, SAC

2.4.	Modified All Treated	SP_NS7	Spider Plot of Percent Change from Baseline in PSA by Prior Treatment (Lx or L2)	Indication of the subject number and dose level will be provided below the plot. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	IA, SAC
2.5.	Modified All Treated	RE8A	Waterfall Plot of Investigator Assessed Maximum Percent Reduction from Baseline in Tumour Measurement in Target Lesions	The plot will be color-coded for best response with confirmation. Indication of the subject number and dose level will be provided below the plot. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
2.6.	Modified All Treated	SP_NS7	Spider Plot of Percent Change from Baseline in Target Tumour Size	Indication of the subject number and dose level will be provided below the plot. By Dose Level for each Arm.	IA, SAC
2.7.	Modified All Treated	SP_NS7	Spider Plot of Percent Change from Baseline in Target Tumour Size by Prior Treatment (Lx or L2)	Indication of the subject number and dose level will be provided below the plot. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	IA, SAC
2.8.	Modified All Treated	RE8A	Waterfall Plot of Percent Change at Maximum Reduction from Baseline in CTC Counts	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
2.9.	Modified All Treated	SP_NS7	Spider Plot of CTC Counts Percent Change from Baseline Over Time	For subjects with unfavourable CTC at baseline. By Dose Level for each Arm.	SAC

				By L2 vs. Lx subgroups and total.	
2.10.	Modified All Treated	TTE10	Kaplan Meier Plot of Radiographic Progression-Free Survival (rPFS)	The plot will be color-coded for dose level for each arm. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC

13.10.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure					
3.1.	All Treated	OEX1	Summary of Exposure to GSK525762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. In OEX1, the time on study treatment categories can be modified if necessary. Duration of exposure=Last dose date – first dose date +1; will be categorized into <3d, 3d-<6d, 6d-<12d, >=12d. Avg. daily dose=cumulative dose / duration of exposure.	DE, IA, SAC
3.2.	All Treated	OEX1	Summary of Exposure to abiraterone	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	DE, SAC

				In OEX1, the time on study treatment categories can be modified if necessary.	
3.3.	All Treated	OEX1	Summary of Exposure to enzalutamide	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. In OEX1, the time on study treatment categories can be modified if necessary.	DE, IA, SAC
3.4.	All Treated	OEX1	Summary of Exposure to abiraterone – Lead in Period	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.5.	All Treated	OEX1	Summary of Exposure to enzalutamide – Lead in Period	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.6.	All Treated	ODMOD1	Summary of Dose Reductions of GSK525762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. May be replaced by a listing if minimal data available.	SAC
3.7.	All Treated	ODMOD1	Summary of Dose Reductions of abiraterone	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. May be replaced by a listing if minimal data available	SAC
3.8.	All Treated	ODMOD1	Summary of Dose Reductions of enzalutamide	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. May be replaced by a listing if minimal data available	SAC

3.9.	All Treated	ODMOD2	Summary of Dose Interruptions/Delays of GSK525762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Categories <7, 7-14, >14 days for duration of interruption	SAC
3.10.	All Treated	ODMOD2	Summary of Dose Interruptions/Delays of abiraterone	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. May be replaced by a listing if minimal data available.	SAC
3.11.	All Treated	ODMOD2	Summary of Dose Interruptions/Delays of enzalutamide	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. May be replaced by a listing if minimal data available.	SAC
3.12.	All Treated	ODMOD8	Summary of Dose Escalations of GSK525762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. May be replaced by a listing if minimal data available.	SAC
3.13.	All Treated	AE19	Summary of Dose-Limiting Toxicities during the Determinative Period	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
Adverse Events					
3.14.	All Treated	AE13	Summary of Adverse Event Overview	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	IA, SAC
3.15.	All Treated	AE3	Summary of Adverse Event Related to Any Study Treatment	By Dose Level for each Arm.	SAC

				By L2 vs. Lx subgroups and total.	
3.16.	All Treated	AE3	Summary of Adverse Event Related to GSK525762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.17.	All Treated	AE13	Summary of Adverse Event of Grade 3-4 Overview	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.18.	All Treated	AE3	Summary of Adverse Event of Grade 3-4 Related to Any Study Treatment	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.19.	All Treated	AE3	Summary of Adverse Event of Grade 3-4 related to GSK525762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.20.	All Treated	AE16	Summary of Adverse Events by System Organ Class and Preferred Term	By Event category, PT, SOC. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	IA, SAC
3.21.	All Treated	AE15	Summary of Common 5% Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences)	By Event category, PT, SOC. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.22.	All Treated	AE5B	Summary of All Adverse Events by Maximum Toxicity Grade by System Organ Class and Preferred Term	Events in Descending Order of Total Incidence. By Event category, PT, SOC. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC

3.23.	All Treated	AE5B	Summary of Any Drug-Related Adverse Events by Maximum Toxicity Grade by System Organ Class and Preferred Term	Events in Descending Order of Total Incidence. By Event category, PT, SOC. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.24.	All Treated	AE5B	Summary of All Adverse Events Related to GSK525762- by Maximum Toxicity Grade by System Organ Class and Preferred Term	Events in Descending Order of Total Incidence. By Event category, PT. Subset for events related to GSk525762 only. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.25.	All Treated	AE5B	Summary of enzalutamide-Related Adverse Events by Maximum Toxicity Grade by System Organ Class and Preferred Term	Events in Descending Order of Total Incidence. By Event category, PT. Subset for events related to GSk525762 only. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.26.	All Treated	AE5B	Summary of abiraterone-Related Adverse Events by Maximum Toxicity Grade by System Organ Class and Preferred Term	Events in Descending Order of Total Incidence. By Event category, PT. Subset for events related to GSk525762 only. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC

3.27.	All Treated	AE3	Summary of Adverse Events Leading to Permanent Discontinuation of GSK525762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	DE, SAC
3.28.	All Treated	AE3	Summary of Adverse Events Leading to Permanent Discontinuation of Any Study Treatment	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.29.	All Treated	AE3	Summary of Adverse Events Leading to Dose Reductions of GSK52762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	DE, SAC
3.30.	All Treated	AE3	Summary of Adverse Events Leading to Dose Reductions of any Study Treatment	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.31.	All Treated	AE3	Summary of Adverse Events Leading to Dose Interruptions/Delays of GSK52762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	DE, SAC
3.32.	All Treated	AE3	Summary of Adverse Events Leading to Dose Interruptions/Delays of Any Study Treatment	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.33.	All Treated	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term	By Event category, PT, SOC. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	DE, IA, SAC
3.34.	All Treated	AE20	Summary of Any Drug-Related Non-Fatal Serious Adverse Events	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.35.	All Treated	AE20	Summary of GSK525762-Related Non-Fatal Serious Adverse Events	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC

3.36.	All Treated	AE3	Summary of Adverse Events Classified as Dose-Limiting Toxicities (DLTs)	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.37.	All Treated	AE5B	Summary of Adverse Events of Special Interest by Maximum Grade by Preferred Term Regardless of Relatedness	Events in Descending Order of Total Incidence. By Event category, PT. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.38.	All Treated	AE5B	Summary of Adverse Events of Special Interest Regardless of Relatedness	By Event category, PT. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	IA, SAC
3.39.	All Treated	ESI1	Summary of Characteristics of Adverse Events of Special Interest	This table will be presented individually for each category of AESI: # subjects, # events, # subjects with SAE, # subjects with related SI events, outcome event, maximum grade, action taken. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.40.	All Treated	ESI2b	Summary of Onset and Duration of the First Occurrence (Days) of Treatment Emergent Adverse Events of Special Interest	This table will be presented individually for each category of AESI: # subjects, # events, # subjects with SAE, # subjects with related SI events, outcome event, maximum grade, action taken.	SAC

				By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	
3.41.	All Treated	DD1	Summary of Deaths	Include number of patients for which an SAE resulted in death.	SAC
Laboratory: Chemistry					
3.42.	All Treated	LB1	Summary of Chemistry Changes from Baseline	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.43.	All Treated	LB18	Summary of Chemistry Grade Changes from Baseline	For lab tests that are not graded include worst case grade change. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.44.	All Treated	LB3	Summary of Chemistry Changes from Baseline with Respect to the Normal Range	For lab tests that are not graded include worst case grade change. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
Laboratory: Haematology					
3.45.	All Treated	LB1	Summary of Haematology Changes from Baseline	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.46.	All Treated	LB18	Summary of Haematology Grade Changes from Baseline	For lab tests that are not graded; include worst case grade change. By Dose Level for each Arm.	SAC

				By L2 vs. Lx subgroups and total.	
3.47.	All Treated	LB3	Summary of Haematology Changes from Baseline with Respect to the Normal Range	For lab tests that are not graded; include worst case grade change. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
Laboratory: Liver Events					
3.48.	All Treated	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.49.	All Treated	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
Urinalysis					
3.50.	All Treated	UR1	Summary of Worst-case Urinalysis Result Increases from Baseline	Include tests done by Dipstick – Specific gravity, pH, Glucose, Protein, Blood, Ketones. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.51.	All Treated	LB18	Summary of Urinalysis Grade Changes from Baseline	For lab tests that are not graded; include worst case grade change. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC

Coagulation					
3.52.	All Treated	LB3	Summary of Coagulation Changes from Baseline with Respect to Normal Range	Include worst case grade change. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
Vital Signs					
3.53.	All Treated	VS1	Summary of Vital Signs	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.54.	All Treated	VS1	Summary of Vital Sign Changes from Baseline	Include all Vital Signs. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
ECG					
3.55.	All Treated	EG1	Summary of ECG Findings	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.56.	All Treated	EG2	Summary of ECG Findings Change from Baseline	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Add footnote: “Only the post-baseline assessments that used the same source (i.e. local or central cardiologist read) as the baseline assessments are used to derive the change from baseline.”	SAC

3.57.	All Treated	EG10A	Summary of Maximum QTcF Value Post-Baseline Relative to Baseline	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Add footnote: "Only the post-baseline assessments that used the same source (i.e. local or central cardiologist read) as the baseline assessments are used to derive the change from baseline."	SAC
3.58.	All Treated	EG11A	Summary of Maximum Increase in QTcF Values Post-Baseline Relative to Baseline	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Add footnote: "Only the post-baseline assessments that used the same source (i.e. local or central cardiologist read) as the baseline assessments are used to derive the change from baseline."	SAC
Performance Status					
3.59.	All Treated	PS1A	Summary of Performance Status	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.60.	All Treated	PS3A	Summary of Change in Performance Status from Baseline	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC

Left Ventricular Ejection Fraction					
3.61.	All Treated	OLVEF1A	Summary of Left Ventricular Ejection Fraction Change from Baseline	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Add footnote: "Only the post-baseline assessments that used the same method (i.e. Electrocardiogram ECHO or Multiple Grated Acquisition MUGA) and the same source (i.e. local or central cardiologist read) as the baseline assessments are used to derive the change from baseline."	SAC
Value Evidence and Outcomes					
3.62.	Modified All Treated	SF4_NS2	Summary of EORTC-QLQ-C30 and Change from Baseline in EORTC-QLQ-C30	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Summarize both Timepoints data and change from baseline at timepoints data in the same output.	SAC
3.63.	Modified All Treated	SF4_NS2	Summary of EORTC-QLQ-PR25 and Change from Baseline in EORTC-QLQ-PR25	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Summarize both Timepoints data and change from baseline at timepoints data in the same output.	SAC

3.64.	Modified All Treated	SF4_NS2	Summary of BPI-SF and Change from Baseline in BPI-SF	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Summarize both Timepoints data and change from baseline at timepoints data in the same output.	SAC
3.65.	Modified All Treated	SF4_NS2	Summary of PRO-CTCAE and Change from Baseline in PRO-CTCAE	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Summarize both Timepoints data and change from baseline at timepoints data in the same output.	SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure					
3.1.	All Treated	OEX1	Summary of Exposure to GSK525762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. In OEX1, the time on study treatment categories can be modified if necessary. Duration of exposure=Last dose date – first dose date +1; will be categorized into <3d, 3d-<6d, 6d-<12d, >=12d. Avg. daily dose=cumulative dose / duration of exposure.	DE, IA, SAC
3.2.	All Treated	OEX1	Summary of Exposure to abiraterone	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. In OEX1, the time on study treatment categories can be modified if necessary.	DE, SAC
3.3.	All Treated	OEX1	Summary of Exposure to enzalutamide	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. In OEX1, the time on study treatment categories can be modified if necessary.	DE, IA, SAC
3.4.	All Treated	OEX1	Summary of Exposure to abiraterone – Lead in Period	By Dose Level for each Arm.	SAC

				By L2 vs. Lx subgroups and total.	
3.5.	All Treated	OEX1	Summary of Exposure to enzalutamide – Lead in Period	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.6.	All Treated	ODMOD1	Summary of Dose Reductions of GSK525762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. May be replaced by a listing if minimal data available.	SAC
3.7.	All Treated	ODMOD1	Summary of Dose Reductions of abiraterone	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. May be replaced by a listing if minimal data available	SAC
3.8.	All Treated	ODMOD1	Summary of Dose Reductions of enzalutamide	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. May be replaced by a listing if minimal data available	SAC
3.9.	All Treated	ODMOD2	Summary of Dose Interruptions/Delays of GSK525762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Categories <7, 7-14, >14 days for duration of interruption	SAC
3.10.	All Treated	ODMOD2	Summary of Dose Interruptions/Delays of abiraterone	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. May be replaced by a listing if minimal data available.	SAC

3.11.	All Treated	ODMOD2	Summary of Dose Interruptions/Delays of enzalutamide	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. May be replaced by a listing if minimal data available.	SAC
3.12.	All Treated	ODMOD8	Summary of Dose Escalations of GSK525762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. May be replaced by a listing if minimal data available.	SAC
3.13.	All Treated	AE19	Summary of Dose-Limiting Toxicities during the Determinative Period	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
Adverse Events					
3.14.	All Treated	AE13	Summary of Adverse Event Overview	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	IA, SAC
3.15.	All Treated	AE3	Summary of Adverse Event Related to Any Study Treatment	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.16.	All Treated	AE3	Summary of Adverse Event Related to GSK525762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.17.	All Treated	AE13	Summary of Adverse Event of Grade 3-4 Overview	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.18.	All Treated	AE3	Summary of Adverse Event of Grade 3-4 Related to Any Study Treatment	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC

3.19.	All Treated	AE3	Summary of Adverse Event of Grade 3-4 related to GSK525762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.20.	All Treated	AE16	Summary of Adverse Events by System Organ Class and Preferred Term	By Event category, PT, SOC. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	IA, SAC
3.21.	All Treated	AE15	Summary of Common 5% Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences)	By Event category, PT, SOC. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.22.	All Treated	AE5B	Summary of All Adverse Events by Maximum Toxicity Grade by System Organ Class and Preferred Term	Events in Descending Order of Total Incidence. By Event category, PT, SOC. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.23.	All Treated	AE5B	Summary of Any Drug-Related Adverse Events by Maximum Toxicity Grade by System Organ Class and Preferred Term	Events in Descending Order of Total Incidence. By Event category, PT, SOC. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.24.	All Treated	AE5B	Summary of All Adverse Events Related to GSK525762- by Maximum Toxicity Grade by System Organ Class and Preferred Term	Events in Descending Order of Total Incidence. By Event category, PT. Subset for events related to GSk525762 only. By Dose Level for each Arm.	SAC

				By L2 vs. Lx subgroups and total.	
3.25.	All Treated	AE5B	Summary of enzalutamide-Related Adverse Events by Maximum Toxicity Grade by System Organ Class and Preferred Term	Events in Descending Order of Total Incidence. By Event category, PT. Subset for events related to GSk525762 only. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.26.	All Treated	AE5B	Summary of abiraterone-Related Adverse Events by Maximum Toxicity Grade by System Organ Class and Preferred Term	Events in Descending Order of Total Incidence. By Event category, PT. Subset for events related to GSk525762 only. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.27.	All Treated	AE3	Summary of Adverse Events Leading to Permanent Discontinuation of GSK525762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	DE, SAC
3.28.	All Treated	AE3	Summary of Adverse Events Leading to Permanent Discontinuation of Any Study Treatment	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.29.	All Treated	AE3	Summary of Adverse Events Leading to Dose Reductions of GSK52762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	DE, SAC
3.30.	All Treated	AE3	Summary of Adverse Events Leading to Dose Reductions of any Study Treatment	By Dose Level for each Arm.	SAC

				By L2 vs. Lx subgroups and total.	
3.31.	All Treated	AE3	Summary of Adverse Events Leading to Dose Interruptions/Delays of GSK52762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	DE, SAC
3.32.	All Treated	AE3	Summary of Adverse Events Leading to Dose Interruptions/Delays of Any Study Treatment	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.33.	All Treated	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term	By Event category, PT, SOC. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	DE, IA, SAC
3.34.	All Treated	AE20	Summary of Any Drug-Related Non-Fatal Serious Adverse Events	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.35.	All Treated	AE20	Summary of GSK525762-Related Non-Fatal Serious Adverse Events	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.36.	All Treated	AE3	Summary of Adverse Events Classified as Dose-Limiting Toxicities (DLTs)	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.37.	All Treated	AE5B	Summary of Adverse Events of Special Interest by Maximum Grade by Preferred Term Regardless of Relatedness	Events in Descending Order of Total Incidence. By Event category, PT. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.38.	All Treated	AE5B	Summary of Adverse Events of Special Interest Regardless of Relatedness	By Event category, PT. By Dose Level for each Arm.	IA, SAC

				By L2 vs. Lx subgroups and total.	
3.39.	All Treated	ESI1	Summary of Characteristics of Adverse Events of Special Interest	This table will be presented individually for each category of AESI: # subjects, # events, # subjects with SAE, # subjects with related SI events, outcome event, maximum grade, action taken. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.40.	All Treated	ESI2b	Summary of Onset and Duration of the First Occurrence (Days) of Treatment Emergent Adverse Events of Special Interest	This table will be presented individually for each category of AESI: # subjects, # events, # subjects with SAE, # subjects with related SI events, outcome event, maximum grade, action taken. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.41.	All Treated	DD1	Summary of Deaths	Include number of patients for which an SAE resulted in death.	SAC
Laboratory: Chemistry					
3.42.	All Treated	LB1	Summary of Chemistry Changes from Baseline	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.43.	All Treated	LB18	Summary of Chemistry Grade Changes from Baseline	For lab tests that are not graded include worst case grade change.	SAC

				By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	
3.44.	All Treated	LB3	Summary of Chemistry Changes from Baseline with Respect to the Normal Range	For lab tests that are not graded include worst case grade change. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
Laboratory: Haematology					
3.45.	All Treated	LB1	Summary of Haematology Changes from Baseline	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.46.	All Treated	LB18	Summary of Haematology Grade Changes from Baseline	For lab tests that are not graded; include worst case grade change. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.47.	All Treated	LB3	Summary of Haematology Changes from Baseline with Respect to the Normal Range	For lab tests that are not graded; include worst case grade change. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
Laboratory: Liver Events					
3.48.	All Treated	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC

3.49.	All Treated	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
Urinalysis					
3.50.	All Treated	UR1	Summary of Worst-case Urinalysis Result Increases from Baseline	Include tests done by Dipstick – Specific gravity, pH, Glucose, Protein, Blood, Ketones. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.51.	All Treated	LB18	Summary of Urinalysis Grade Changes from Baseline	For lab tests that are not graded; include worst case grade change. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC

Coagulation					
3.52.	All Treated	LB3	Summary of Coagulation Changes from Baseline with Respect to Normal Range	Include worst case grade change. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
Vital Signs					
3.53.	All Treated	VS1	Summary of Vital Signs	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.54.	All Treated	VS1	Summary of Vital Sign Changes from Baseline	Include all Vital Signs. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
ECG					
3.55.	All Treated	EG1	Summary of ECG Findings	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.56.	All Treated	EG2	Summary of ECG Findings Change from Baseline	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Add footnote: “Only the post-baseline assessments that used the same source (i.e. local or central cardiologist read) as the baseline assessments are used to derive the change from baseline.”	SAC

3.57.	All Treated	EG10A	Summary of Maximum QTcF Value Post-Baseline Relative to Baseline	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Add footnote: "Only the post-baseline assessments that used the same source (i.e. local or central cardiologist read) as the baseline assessments are used to derive the change from baseline."	SAC
3.58.	All Treated	EG11A	Summary of Maximum Increase in QTcF Values Post-Baseline Relative to Baseline	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Add footnote: "Only the post-baseline assessments that used the same source (i.e. local or central cardiologist read) as the baseline assessments are used to derive the change from baseline."	SAC
Performance Status					
3.59.	All Treated	PS1A	Summary of Performance Status	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.60.	All Treated	PS3A	Summary of Change in Performance Status from Baseline	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC

Left Ventricular Ejection Fraction					
3.61.	All Treated	OLVEF1A	Summary of Left Ventricular Ejection Fraction Change from Baseline	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Add footnote: "Only the post-baseline assessments that used the same method (i.e. Electrocardiogram ECHO or Multiple Grated Acquisition MUGA) and the same source (i.e. local or central cardiologist read) as the baseline assessments are used to derive the change from baseline."	SAC
Value Evidence and Outcomes					
3.62.	Modified All Treated	SF4_NS2	Summary of EORTC-QLQ-C30 and Change from Baseline in EORTC-QLQ-C30	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Summarize both Timepoints data and change from baseline at timepoints data in the same output.	SAC
3.63.	Modified All Treated	SF4_NS2	Summary of EORTC-QLQ-PR25 and Change from Baseline in EORTC-QLQ-PR25	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Summarize both Timepoints data and change from baseline at timepoints data in the same output.	SAC

3.64.	Modified All Treated	SF4_NS2	Summary of BPI-SF and Change from Baseline in BPI-SF	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Summarize both Timepoints data and change from baseline at timepoints data in the same output.	SAC
3.65.	Modified All Treated	SF4_NS2	Summary of PRO-CTCAE and Change from Baseline in PRO-CTCAE	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Summarize both Timepoints data and change from baseline at timepoints data in the same output.	SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure					
3.1.	All Treated	OEX1	Summary of Exposure to GSK525762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. In OEX1, the time on study treatment categories can be modified if necessary. Duration of exposure=Last dose date – first dose date +1; will be categorized into <3d, 3d-<6d, 6d-<12d, >=12d. Avg. daily dose=cumulative dose / duration of exposure.	DE, IA, SAC
3.2.	All Treated	OEX1	Summary of Exposure to abiraterone	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. In OEX1, the time on study treatment categories can be modified if necessary.	DE, SAC
3.3.	All Treated	OEX1	Summary of Exposure to enzalutamide	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. In OEX1, the time on study treatment categories can be modified if necessary.	DE, IA, SAC
3.4.	All Treated	OEX1	Summary of Exposure to abiraterone – Lead in Period	By Dose Level for each Arm.	SAC

				By L2 vs. Lx subgroups and total.	
3.5.	All Treated	OEX1	Summary of Exposure to enzalutamide – Lead in Period	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.6.	All Treated	ODMOD1	Summary of Dose Reductions of GSK525762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. May be replaced by a listing if minimal data available.	SAC
3.7.	All Treated	ODMOD1	Summary of Dose Reductions of abiraterone	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. May be replaced by a listing if minimal data available	SAC
3.8.	All Treated	ODMOD1	Summary of Dose Reductions of enzalutamide	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. May be replaced by a listing if minimal data available	SAC
3.9.	All Treated	ODMOD2	Summary of Dose Interruptions/Delays of GSK525762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Categories <7, 7-14, >14 days for duration of interruption	SAC
3.10.	All Treated	ODMOD2	Summary of Dose Interruptions/Delays of abiraterone	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. May be replaced by a listing if minimal data available.	SAC

3.11.	All Treated	ODMOD2	Summary of Dose Interruptions/Delays of enzalutamide	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. May be replaced by a listing if minimal data available.	SAC
3.12.	All Treated	ODMOD8	Summary of Dose Escalations of GSK525762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. May be replaced by a listing if minimal data available.	SAC
3.13.	All Treated	AE19	Summary of Dose-Limiting Toxicities during the Determinative Period	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
Adverse Events					
3.14.	All Treated	AE13	Summary of Adverse Event Overview	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	IA, SAC
3.15.	All Treated	AE3	Summary of Adverse Event Related to Any Study Treatment	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.16.	All Treated	AE3	Summary of Adverse Event Related to GSK525762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.17.	All Treated	AE13	Summary of Adverse Event of Grade 3-4 Overview	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.18.	All Treated	AE3	Summary of Adverse Event of Grade 3-4 Related to Any Study Treatment	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC

3.19.	All Treated	AE3	Summary of Adverse Event of Grade 3-4 related to GSK525762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.20.	All Treated	AE16	Summary of Adverse Events by System Organ Class and Preferred Term	By Event category, PT, SOC. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	IA, SAC
3.21.	All Treated	AE15	Summary of Common 5% Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences)	By Event category, PT, SOC. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.22.	All Treated	AE5B	Summary of All Adverse Events by Maximum Toxicity Grade by System Organ Class and Preferred Term	Events in Descending Order of Total Incidence. By Event category, PT, SOC. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.23.	All Treated	AE5B	Summary of Any Drug-Related Adverse Events by Maximum Toxicity Grade by System Organ Class and Preferred Term	Events in Descending Order of Total Incidence. By Event category, PT, SOC. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.24.	All Treated	AE5B	Summary of All Adverse Events Related to GSK525762- by Maximum Toxicity Grade by System Organ Class and Preferred Term	Events in Descending Order of Total Incidence. By Event category, PT. Subset for events related to GSk525762 only. By Dose Level for each Arm.	SAC

				By L2 vs. Lx subgroups and total.	
3.25.	All Treated	AE5B	Summary of enzalutamide-Related Adverse Events by Maximum Toxicity Grade by System Organ Class and Preferred Term	Events in Descending Order of Total Incidence. By Event category, PT. Subset for events related to GSk525762 only. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.26.	All Treated	AE5B	Summary of abiraterone-Related Adverse Events by Maximum Toxicity Grade by System Organ Class and Preferred Term	Events in Descending Order of Total Incidence. By Event category, PT. Subset for events related to GSk525762 only. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.27.	All Treated	AE3	Summary of Adverse Events Leading to Permanent Discontinuation of GSK525762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	DE, SAC
3.28.	All Treated	AE3	Summary of Adverse Events Leading to Permanent Discontinuation of Any Study Treatment	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.29.	All Treated	AE3	Summary of Adverse Events Leading to Dose Reductions of GSK52762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	DE, SAC
3.30.	All Treated	AE3	Summary of Adverse Events Leading to Dose Reductions of any Study Treatment	By Dose Level for each Arm.	SAC

				By L2 vs. Lx subgroups and total.	
3.31.	All Treated	AE3	Summary of Adverse Events Leading to Dose Interruptions/Delays of GSK52762	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	DE, SAC
3.32.	All Treated	AE3	Summary of Adverse Events Leading to Dose Interruptions/Delays of Any Study Treatment	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.33.	All Treated	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term	By Event category, PT, SOC. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	DE, IA, SAC
3.34.	All Treated	AE20	Summary of Any Drug-Related Non-Fatal Serious Adverse Events	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.35.	All Treated	AE20	Summary of GSK525762-Related Non-Fatal Serious Adverse Events	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.36.	All Treated	AE3	Summary of Adverse Events Classified as Dose-Limiting Toxicities (DLTs)	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.37.	All Treated	AE5B	Summary of Adverse Events of Special Interest by Maximum Grade by Preferred Term Regardless of Relatedness	Events in Descending Order of Total Incidence. By Event category, PT. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.38.	All Treated	AE5B	Summary of Adverse Events of Special Interest Regardless of Relatedness	By Event category, PT. By Dose Level for each Arm.	IA, SAC

				By L2 vs. Lx subgroups and total.	
3.39.	All Treated	ESI1	Summary of Characteristics of Adverse Events of Special Interest	This table will be presented individually for each category of AESI: # subjects, # events, # subjects with SAE, # subjects with related SI events, outcome event, maximum grade, action taken. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.40.	All Treated	ESI2b	Summary of Onset and Duration of the First Occurrence (Days) of Treatment Emergent Adverse Events of Special Interest	This table will be presented individually for each category of AESI: # subjects, # events, # subjects with SAE, # subjects with related SI events, outcome event, maximum grade, action taken. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.41.	All Treated	DD1	Summary of Deaths	Include number of patients for which an SAE resulted in death.	SAC
Laboratory: Chemistry					
3.42.	All Treated	LB1	Summary of Chemistry Changes from Baseline	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.43.	All Treated	LB18	Summary of Chemistry Grade Changes from Baseline	For lab tests that are not graded include worst case grade change.	SAC

				By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	
3.44.	All Treated	LB3	Summary of Chemistry Changes from Baseline with Respect to the Normal Range	For lab tests that are not graded include worst case grade change. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
Laboratory: Haematology					
3.45.	All Treated	LB1	Summary of Haematology Changes from Baseline	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.46.	All Treated	LB18	Summary of Haematology Grade Changes from Baseline	For lab tests that are not graded; include worst case grade change. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.47.	All Treated	LB3	Summary of Haematology Changes from Baseline with Respect to the Normal Range	For lab tests that are not graded; include worst case grade change. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
Laboratory: Liver Events					
3.48.	All Treated	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC

3.49.	All Treated	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
Urinalysis					
3.50.	All Treated	UR1	Summary of Worst-case Urinalysis Result Increases from Baseline	Include tests done by Dipstick – Specific gravity, pH, Glucose, Protein, Blood, Ketones. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.51.	All Treated	LB18	Summary of Urinalysis Grade Changes from Baseline	For lab tests that are not graded; include worst case grade change. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC

Coagulation					
3.52.	All Treated	LB3	Summary of Coagulation Changes from Baseline with Respect to Normal Range	Include worst case grade change. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
Vital Signs					
3.53.	All Treated	VS1	Summary of Vital Signs	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.54.	All Treated	VS1	Summary of Vital Sign Changes from Baseline	Include all Vital Signs. By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
ECG					
3.55.	All Treated	EG1	Summary of ECG Findings	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.56.	All Treated	EG2	Summary of ECG Findings Change from Baseline	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Add footnote: “Only the post-baseline assessments that used the same source (i.e. local or central cardiologist read) as the baseline assessments are used to derive the change from baseline.”	SAC

3.57.	All Treated	EG10A	Summary of Maximum QTcF Value Post-Baseline Relative to Baseline	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Add footnote: "Only the post-baseline assessments that used the same source (i.e. local or central cardiologist read) as the baseline assessments are used to derive the change from baseline."	SAC
3.58.	All Treated	EG11A	Summary of Maximum Increase in QTcF Values Post-Baseline Relative to Baseline	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Add footnote: "Only the post-baseline assessments that used the same source (i.e. local or central cardiologist read) as the baseline assessments are used to derive the change from baseline."	SAC
Performance Status					
3.59.	All Treated	PS1A	Summary of Performance Status	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC
3.60.	All Treated	PS3A	Summary of Change in Performance Status from Baseline	By Dose Level for each Arm. By L2 vs. Lx subgroups and total.	SAC

Left Ventricular Ejection Fraction					
3.61.	All Treated	OLVEF1A	Summary of Left Ventricular Ejection Fraction Change from Baseline	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Add footnote: "Only the post-baseline assessments that used the same method (i.e. Electrocardiogram ECHO or Multiple Grated Acquisition MUGA) and the same source (i.e. local or central cardiologist read) as the baseline assessments are used to derive the change from baseline."	SAC
Value Evidence and Outcomes					
3.62.	Modified All Treated	SF4_NS2	Summary of EORTC-QLQ-C30 and Change from Baseline in EORTC-QLQ-C30	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Summarize both Timepoints data and change from baseline at timepoints data in the same output.	SAC
3.63.	Modified All Treated	SF4_NS2	Summary of EORTC-QLQ-PR25 and Change from Baseline in EORTC-QLQ-PR25	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Summarize both Timepoints data and change from baseline at timepoints data in the same output.	SAC

3.64.	Modified All Treated	SF4_NS2	Summary of BPI-SF and Change from Baseline in BPI-SF	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Summarize both Timepoints data and change from baseline at timepoints data in the same output.	SAC
3.65.	Modified All Treated	SF4_NS2	Summary of PRO-CTCAE and Change from Baseline in PRO-CTCAE	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. Summarize both Timepoints data and change from baseline at timepoints data in the same output.	SAC

13.10.8. Pharmacokinetic Tables

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Drug Concentration Measure					
4.1.	PK	PK01	Summary of GSK525762 Pharmacokinetic Concentration-Time Data	By Arm.	DE, SAC
4.2.	PK	PK01	Summary of GSK525762- active metabolite (GSK3529246) Pharmacokinetic Concentration-Time Data	By Arm.	DE, SAC
4.3.	PK	PK01	Summary of GSK525762 Total Active Moiety Pharmacokinetic Concentration-Time Data (in nM)	GSK525762+GSK3529246. By Arm.	DE, SAC

4.4.	PK	PK01	Summary of abiraterone Pharmacokinetic Concentration-Time Data		DE, SAC
4.5.	PK	PK01	Summary of enzalutamide Pharmacokinetic Concentration-Time Data	Summary will be presented only for pre-dose as samples are collected only at Pre-dose.	DE, SAC
4.6.	PK	PK01	Summary of Enzalutamide active metabolite Pharmacokinetic Concentration-Time Data	Summary will be presented only for pre-dose as samples are collected only at Pre-dose.	
Pharmacokinetic Parameters					
4.7.	PK	PK06	Summary of Derived GSK525762 Pharmacokinetic Parameters	By Dose Level for each Arm. PK parameters: AUC (0-τ) in ng.hr/mL, Cmax in ng/mL, Tmax in h, Ctrough in ng/mL	DE, SAC
4.8.	PK	PK06	Summary of Derived GSK525762 Active Metabolite (GSK3529246) Pharmacokinetic Parameters	By Dose Level for each Arm. PK parameters: AUC (0-τ) in ng.h/mL, Cmax in ng/mL, Tmax in h, Ctrough in ng/mL	DE, SAC
4.9.	PK	PK06	Summary of Derived GSK525762 Total Active Moiety Pharmacokinetic Parameters	By Dose Level for each Arm. PK parameters: AUC (0-τ) in mol.h/L, Cmax in nmol/L, Tmax in h, Ctrough in nmol/L	DE, SAC
4.10.	PK	PK06	Summary of Derived abiraterone Pharmacokinetic Parameters	Only Ctrough (ng/mL)	SAC
4.11.	PK	PK06	Summary of Derived enzalutamide Pharmacokinetic Parameters	Only Ctrough (ng/mL)	SAC
4.12.	PK	PK06	Summary of Derived enzalutamide Active Metabolite Pharmacokinetic Parameters	Only Ctrough (ng/mL)	SAC
4.13.	PK	PK06	Summary of Derived enzalutamide Total Active Moiety Pharmacokinetic Parameters	Only Ctrough (ng/mL)	SAC

13.10.9. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Drug Concentration Measure					
4.1.	PK	PK17	Mean GSK525762, GSK3529246, and the total active moiety Concentration-Time Plots (Linear and Semi-Log)	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. GSK525762, GSK3529246, and the total active moiety concentration-time profiles will be overlaid on the same plot once concentrations have been converted to nM concentrations	DE, SAC
4.2.	PK	PK17	Mean abiraterone Concentration-Time Plots (Linear and Semi-Log)		DE, AC
4.3.	PK	PK18	Median GSK525762, GSK3529246, and the total active moiety Concentration-Time Plots (Linear and Semi-Log)	By Dose Level for each Arm. By L2 vs. Lx subgroups and total. GSK525762, GSK3529246, and the total active moiety concentration-time profiles will be overlaid on the same plot once concentrations have been converted to nM concentrations	SAC
4.4.	PK	PK18	Median abiraterone Concentration-Time Plots (Linear and Semi-Log)		SAC

13.10.10. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	All Treated	ES2	Listing of Reasons for Subject Withdrawal		DE, SAC
2.	All Screened	ES7	Listing of Reasons for Screen Failure		SAC
3.	All Treated	ES7	Listing of Run-in Failure		SAC
4.	All Treated	SD2	Listing of Reasons for Study Treatment Discontinuation	Include last dose date	SAC
Populations Analysed					
5.	All Treated	SP3	Listing of Subjects Excluded from Any Population		SAC
Protocol Deviations					
6.	All Treated	DV2	Listing of Protocol Deviations	Include both major and non-major PDs	SAC
7.	All Treated	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
Baseline and Disease Characteristics					
8.	All Treated	DM2	Listing of Demographic Characteristics		SAC
9.	All Treated	DM9	Listing of Race		SAC
Exposure					
10.	All Treated	TA1	Listing of Planned and Actual Treatments		SAC
11.	All Treated	COMP3C	Listing of GSK525762 Drug Accountability		SAC
12.	All Treated	OEX3a	Listing of Exposure Data to GSK525762		SAC
13.	All Treated	OEX8B	Listing of Exposure Data to abiraterone		SAC
14.	All Treated	OEX8B	Listing of Exposure Data to enzalutamide		SAC

15.	All Treated	ODMOD10A	Listing of Dose Reductions for GSK525762		SAC
16.	All Treated	ODMOD10A	Listing of Dose Reductions for abiraterone		SAC
17.	All Treated	ODMOD10A	Listing of Dose Reductions for enzalutamide		SAC
18.	All Treated	ODMOD11A	Listing of Dose Interruptions/Delays for GSK525762		SAC
19.	All Treated	ODMOD11A	Listing of Dose Interruptions/Delays for abiraterone		SAC
20.	All Treated	ODMOD11A	Listing of Dose Interruptions/Delays for enzalutamide		SAC
21.	All Treated	ODMOD15A	Listing of Dose Escalations for GSK525762		SAC
Adverse Events					
22.	All Treated	OAE04	Listing of All Adverse Events		DE, SAC
23.	All Treated	OAE04	Listing of All AEs by Severity Grade		SAC
24.	All Treated	OAE03	Listing of Subject Numbers for Individual Adverse Events		SAC
25.	All Treated	OAE04	Listing of Dose-Limiting Adverse Events		DE, SAC
26.	All Treated	AE2	Listing of Relationship Between Adverse Event System Organ Class, Preferred Term and Verbatim Text		SAC
Serious and Other Significant Adverse Events					
27.	All Treated	OAE04	Listing of Fatal Serious Adverse Events		DE, SAC
28.	All Treated	OAE04	Listing of Non-Fatal Serious Adverse Events		SAC
29.	All Treated	OAE04	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment	Based on Action taken question on AE/SAE	DE, SAC
30.	All Treated	OAE04	Listing of Adverse Events Leading to Withdrawal from the Study		SAC
31.	All Treated	OAE04	Listing of Adverse Events Leading to Dose Reductions for any Study Drug		DE, SAC
32.	All Treated	OAE04	Listing of Adverse Events Leading to Dose Interruptions/Delays for any Study Drug		DE, SAC
33.	All Treated	AE14	Listing of Reasons for Considering as a Serious Adverse Event		SAC
34.	All Treated	OAE04	Listing of Adverse Events of Special Interest		SAC

Dose-Limiting Toxicity					
35.	All Treated	DL3	Listing of Dose-Limiting Toxicities during the Determinative Period		DE, SAC
Laboratory					
36.	All Treated	OLB7	Listing of Chemistry Laboratory Data for Subjects with Lab Values Outside of Normal Range		SAC
37.	All Treated	OLB7	Listing of Haematology Laboratory Data for Subjects with Lab Values Outside of Normal Range		SAC
38.	All Treated	UR2A	Listing of Urinalysis Data for Subjects with Any Value of Potential Clinical Importance		SAC
39.	All Treated	LB13	Listing of Coagulation and Other Laboratory data		SAC
40.	All Treated	OLB7	Listing of Coagulation and Other Laboratory Data for Subjects with Lab Values Outside of Normal Range		SAC
41.	All Treated	LB14	Listing of Laboratory Data with Character Results		SAC
Pharmacokinetic					
42.	PK	PK07	Listing of GSK525762 Pharmacokinetic Concentration-Time Data		SAC
43.	PK	PK07	Listing of abiraterone Pharmacokinetic Concentration-Time Data		SAC
44.	PK	PK07	Listing of enzalutamide Pharmacokinetic Concentration-Time Data		SAC
45.	PK	PK07	Listing of GSK525762 Active Metabolite (GSK3529246) Pharmacokinetic Concentration-Time Data		SAC
46.	PK	PK07	Listing of enzalutamide Active Metabolite Pharmacokinetic Concentration-Time Data		SAC
47.	PK	PK07	Listing of GSK525762 Total Active Moiety Pharmacokinetic Concentration-Time Data		SAC
48.	PK	PK13	Listing of Derived GSK525762 Pharmacokinetic Parameters		SAC

49.	PK	PK13	Listing of Derived GSK525762 Total Active Moiety Pharmacokinetic Parameters		SAC
50.	PK	PK13	Listing of Derived GSK525762 Active Metabolite (GSK3529246) Pharmacokinetic Parameters		SAC
Efficacy					
51.	Modified All Treated	RE2	Listing of PSA Values by Visit	Include change from baseline, % change from baseline	SAC
52.	Modified All Treated	RE12	Listing of Subject Best Response for Interim Review by First Dose Date		IA
53.	Modified All Treated	LA2	Listing of Investigator-Assessed Target Lesions (RECIST 1.1 Criteria)		SAC
54.	Modified All Treated	LA3	Listing of Investigator-Assessed Non-Target Lesions (RECIST 1.1 Criteria)		SAC
55.	Modified All Treated	LA4	Listing of Investigator-Assessed New Lesions (RECIST 1.1 Criteria)		SAC
56.	Modified All Treated	RE5	Listing of Investigator - Assessed Responses (With and Without Confirmation) (RECIST 1.1)	Include an additional row at the end of each subject for Best Response without confirmation.	SAC
57.	Modified All Treated	RE2	Listing of CTC Counts by Visit	Include change from baseline, % change from baseline	SAC
58.	Modified All Treated	TTE9	Listing of Time to Disease Progression		SAC

13.10.11. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Demographic and Baseline Characteristics					
59.	All Treated	SU2	Listing of Substance Use		SAC
60.	All Treated	DC3	Listing of Disease Characteristics at Initial Diagnosis		SAC
61.	All Treated	DC4	Listing of Disease Characteristics at Screening		SAC
62.	All Treated	MD2	Listing of Metastatic Disease at Screening		SAC
Prior and Concomitant Medication					
63.	All Treated	MH2	Listing of Medical Conditions	Include Prior and Current. Status column will indicate the same	SAC
64.	All Treated	CM2	Listing of Concomitant Medications		DE, SAC
65.	All Treated	BP4	Listing of Blood Products or Blood Supportive Care Products	Include Prior (BP4) and on treatment (BP5)	SAC
66.	All Treated	OSP3	Listing of Surgical Procedures		SAC
67.	All Treated	AE2	Listing of Relationship Between ATC Level1, Ingredient and Verbatim Text		SAC
Anti-Cancer Therapy					
68.	All Treated	AC6	Listing of Anti-Cancer Therapy	Including Prior and Subsequent	IA, SAC
69.	All Treated	AC7	Listing of Anti-Cancer Radiotherapy	Including Prior and Subsequent	SAC
70.	All Treated	AC7	Listing of Surgical Procedures	Including on treatment and follow-up	SAC

ECG					
71.	All Treated	EG5	Listing of All ECG Findings for Subjects with an Abnormal Finding		SAC
72.	All Treated	EG3	Listing of ECG Values for Subjects with Abnormal Values		SAC
Vital Signs					
73.	All Treated	VS4	Listing of Vital Signs		DE, SAC
74.	All Treated	OVT7A	Listing of Vital Signs with Abnormal Values		SAC
LVEF					
75.	All Treated	OLVEF2A	Listing of Left Ventricular Ejection Fraction Results		SAC
Laboratory					
76.	All Treated	OLB13	Listing of Laboratory Data with Character Results		SAC
Value Evidence and Outcomes					
77.	Modified All Treated	SF6	Listing of EORTC-QLQ-C30		SAC
78.	Modified All Treated	SF6	Listing of EORTC-QLQ-PR25		SAC
79.	Modified All Treated	BPI4	Listing of BPI-SF		SAC
80.	Modified All Treated	SF6	Listing of PRO-CTCAE		SAC

13.11. Appendix 11: Example Mock Shells for Data Displays

Data Display Specification will be made available on Request.