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

Title	:	Reporting and Analysis Plan for a Phase I/II Dose Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of GSK525762 in Combination with Fulvestrant in Subjects with Hormone Receptor-Positive/HER2-Negative (HR+/HER2-) Advanced or Metastatic Breast Cancer.
Compound Number	:	GSK525762
Effective Date	:	11-AUG-2020

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Phase I Clinical Study Report for Protocol 201973. This includes the Primary Clinical Study Report (CSR) and any End-of-Study outputs that will be generated.
- This RAP is intended to describe the planned efficacy, safety and pharmacokinetics analyses required for Phase I of the study.
- This RAP will be provided to the study team members to convey the content of Phase I data review and interim analysis deliverables, as well as to provide details of the Statistical Analysis Complete (SAC) deliverable.

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1. INTRODUCTION

The purpose of this RAP is to describe the analyses to be performed in support of the Clinical Study Report for GSK Protocol 201973.

Revision Chronology:		
Original	11-AUG-2016	2015N238773_00
Amendment No. 1	21-OCT-2016	2015N238773_01
Amendment No. 2	31-JAN2017	2015N238773_02
Amendment No. 3	07-MAR-2017	2015N238773_03
Amendment No. 4	18-OCT-2017	2015N238773_04
Amendment No. 5	11-SEP-2018	2015N238773_05
Amendment No. 6	06-MAY-2020	2015N238773_06

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.

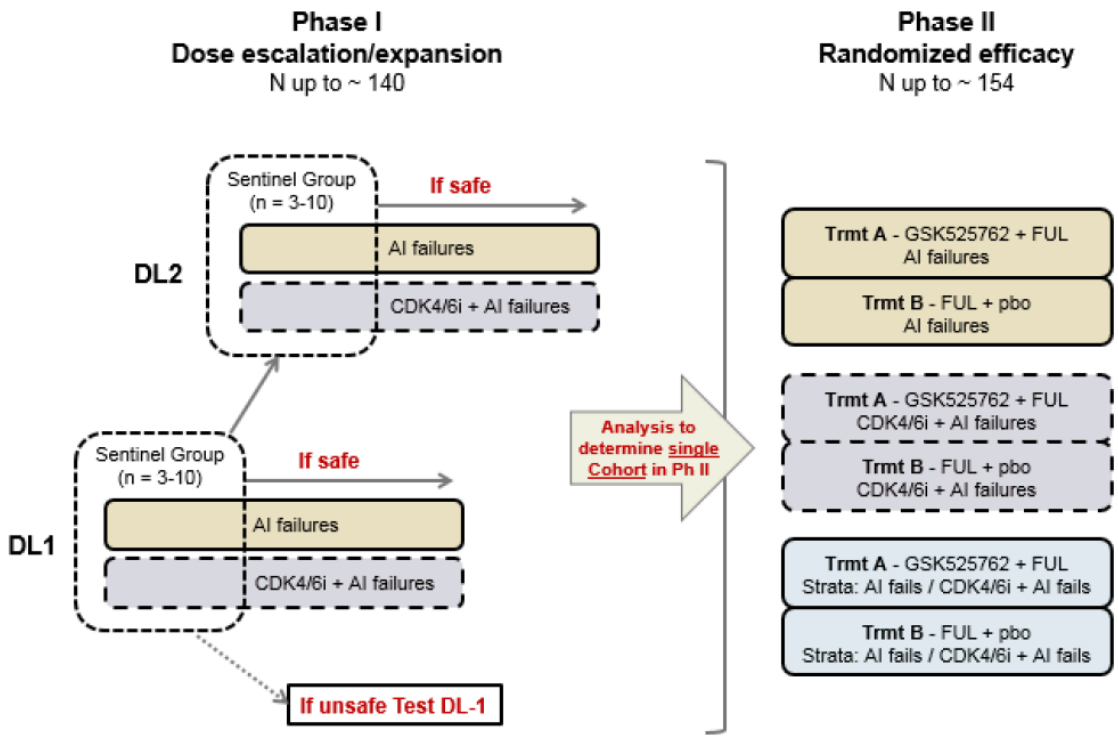
2.2. Study Objective(s) and Endpoint(s)

Objectives	**Endpoints**
Primary Objectives	**Primary Endpoints**
• To determine a recommended Phase 2 dose (RP2D) of GSK525752, when given in combination with fulvestrant, in women with advanced or metastatic hormone receptor-positive/HER2-negative breast cancer (HR+/HER2− BC).	• Safety profile (e.g., adverse events [AEs], serious adverse events [SAEs], dose-limiting toxicities [DLTs], dose reductions or delays), overall response rate (ORR; defined as complete response [CR] rate plus partial response [PR] rate), pharmacokinetic (PK) parameters.
Secondary Objectives	**Secondary Endpoints**
• To determine the safety, tolerability and maximum tolerated dose (MTD) of GSK525762, when given in combination with fulvestrant in women with advanced or metastatic HR+/HER2− BC.	• AEs, 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 evaluate clinical activity of GSK525762 and fulvestrant, when given in combination, in women with advanced or metastatic HR+/HER2− BC.	• Disease control rate (DCR; defined as rate of CR plus PR plus stable disease [SD]), duration of response (DoR), and progression-free survival (PFS).

Objectives	Endpoints
• To characterize the exposure to GSK525762 and fulvestrant, when given in combination, in women with advanced or metastatic HR+/HER2− BC.	• Concentrations of GSK525762, GSK525762 relevant metabolites, and fulvestrant following administration in combination.
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate additional measures of clinical activity of GSK525762 and fulvestrant, when given in combination, in women with advanced or metastatic HR+/HER2− BC.	• Overall survival (OS).
• To characterize the pharmacodynamics of GSK525762 and fulvestrant, when given in combination, in women with advanced or metastatic HR+/HER2− BC.	• Transcriptomic and/or protein changes in molecular markers of BET inhibition and HR signalling in tumor tissue. (Analyses may not be conducted if insufficient sample size.)
• To identify potential indicators of sensitivity or response to GSK525762 and fulvestrant, when given in combination, in women with advanced or metastatic HR+/HER2− BC.	• Mutational analysis of tumor tissue; correlation of baseline somatic and tumor-specific genetic and genomic profiles with response. (Analyses may not be conducted if insufficient sample size.)
• To describe the kinetics of tumor growth in the presence of GSK525762 and fulvestrant for each treatment and investigate the relationship between tumor growth kinetics and clinical activity.	• Tumor size over time, tumor growth rate constants, and time to tumor growth, predicted by the model parameters defining relationships with clinical activity parameters.
• To evaluate the exposure-response relationship between GSK525762 and/or fulvestrant exposure and safety and efficacy parameters.	• Relationship between GSK525762 and/or fulvestrant exposure markers (e.g., dose, C_{min}, C_{max}), and safety and efficacy parameters.
• To evaluate the effect of GSK525762 and fulvestrant, when given in combination, on symptoms and quality of life.	• Change from baseline in EORTC-QLQ-C30 and EORTC-QLQ-BR23 questionnaires. Changes from baseline in select items from the PRO-CTCAE.
• To evaluate ESR1 mutational status as a potential indicator of sensitivity and/or response to GSK525762 and fulvestrant, when given in combination, in women with advanced or metastatic HR+/HER2− BC.	• Targeted sequencing to determine correlation between ESR1 mutations and clinical response.

2.3. Study Design

Overview of Study Design and Key Features



Cohorts may be stopped at any time for toxicity or futility after 10 subjects enrolled

Design Features	• Phase I of the study is designed as a parallel, single-arm, dose escalation/expansion phase to determine the RP2D based on safety, tolerability, PK and efficacy profiles observed after oral administration of GSK525762 in combination with fulvestrant, in advanced or metastatic HR+/HER2− BC subjects. The combination of GSK525762 plus fulvestrant will be evaluated in an open-label fashion in separate populations (i.e., cohorts) of subjects. Subjects will be enrolled into one of the following cohorts based on treatment history: 1. Cohort 1 – Subjects with disease that relapsed during prior treatment or within 12 months after completing adjuvant therapy with an aromatase inhibitor (AI), or disease that progressed during prior treatment with an AI for advanced/metastatic disease. Prior ovarian suppression and/or tamoxifen are allowed, given all other criteria are met. 2. Cohort 2 – Subjects with disease that progressed during prior treatment with the combination of a CDK4/6 inhibitor (e.g., palbociclib) plus letrozole for advanced/metastatic disease. Prior ovarian suppression and/or tamoxifen are allowed, given all other criteria are met. • Phase I will follow a modified toxicity probability interval (mTPI) design, assuming (a) approximately 30 subjects will complete the DLT evaluation period and (b) the true underlying toxicity rate for GSK525762 in

Overview of Study Design and Key Features	
	combination with fulvestrant falls within the range of 25% to 35%, centered at 30%. • Cohort 1 may enrol up to 35 subjects, while Cohort 2 may enrol up to 32 subjects. However, the total number of subjects enrolled into each cohort may vary, as interim analyses for safety and efficacy may terminate enrolment within a cohort if the observed DLT rate exceeds the maximum permitted toxicity rate per the mTPI, or if the efficacy rate does not exceed the historical ORR. • Dosing will begin at dose level 1 (DL1), with subjects administered GSK525762 at 60 mg orally once daily and fulvestrant at 500 mg intramuscularly (IM) on Days 1, 15 and 29 of Cycle 1 and then monthly thereafter. Subjects will be enrolled into cohorts based on their treatment history. Once three evaluable subjects (total, irrespective of cohort) have cleared the DLT evaluation period of 28 days, then an mTPI method will be used to determine whether to dose escalate to DL2 (if there is no DLT), reduce dose to DL-1 (if there are two or three DLTs), or continue enrolling subjects at DL1 (if there is one DLT). Up to 10 additional subjects may be enrolled in groups of approximately three at DL1 prior to a final dose escalation/de-escalation decision. If DL-1 is tested and found to be safe, then re-evaluation of DL1 may be attempted, if guided by the model. If both DL-1 and DL1 are being evaluated, then subjects will be randomized 1:1 to either DL-1 or DL1. • Once a sentinel group of 3-10 evaluable subjects has cleared the DLT evaluation period of 28 days at DL1, the two cohorts will open at DL2. The DL2 DLT evaluation will occur as described for DL1, with a sentinel group of 3-10 evaluable subjects spread across the two cohorts. • For each cohort, enrolment within the cohort may be stopped due to futility if the Bayesian predictive probability of confirmed response rate ≥25% (target) is small. Guidelines for interim futility analysis decision rules for the 10th through 34th evaluable subject are presented in Section 3.1.2.1, Interim Futility Analysis. The guidelines specify the number of subjects with confirmed responses needed for continued enrolment versus stopping for futility when the total sample size is ≤34 subjects in the cohort. • The decision to proceed to Phase II will be based on the totality of data from Phase I, including safety, efficacy and PK data. • While the overall study goals and design remain the same, changes have been made to Phase I of the study in order to address the emerging data and better define the patient population most likely to benefit from the combination treatment of GSK525762 plus fulvestrant. The following are to be noted: 1. DL1 Cohort 1 (60 mg, AI failures) will enrol up to 35 subjects, as per Protocol Amendment 5. 2. DL1 Cohort 2 (60 mg, CDK4/6 + AI failure) – change in inclusion criteria and to the number of subjects to be enrolled is detailed below.

Overview of Study Design and Key Features	
	3. DL2 (80 mg) both cohorts (Cohort 1 and Cohort 2) – enrolment is closed based on decreased tolerability and lack of efficacy, as per protocol guidance. • Enrolment into DL1 (60mg) Cohort 2 is modified. Subjects previously treated with the combination of a CDK4/6 inhibitor (e.g., palbociclib) plus AI for advanced or metastatic disease will be enrolled as follows: o Up to 32 subjects with measurable disease who have progressed after greater than or equal to 12 months of prior treatment with CDK4/6 inhibitor plus AI. o Up to 16 subjects with bone only disease who have progressed after greater than or equal to 12 months of prior treatment with CDK4/6 inhibitor plus AI. o Prior ovarian suppression and/or tamoxifen will be allowed, given all other criteria are met.
Dosing	The projected dose levels of GSK525762 for Phase I dose escalation are 60 mg (DL1) and 80 mg (DL2), each administered orally once daily. If unacceptable toxicity is observed at 60 mg, then 40 mg once daily may be explored (referred to as DL-1). The projected dose level of fulvestrant is the approved dose regimen of 500 mg IM on Days 1, 15 and 29 of Cycle 1 and then monthly thereafter.
Time and Events	Refer to Tables 4 and 5 in Section 7.1 of the Protocol.
Treatment Assignment	Study Phase I is an open label, single-arm phase. If one dose level is open for enrolment, subjects will be assigned to the dose at that level. If more than one dose level is open for enrolment, subjects will be randomly assigned to one of the open dose levels with 1:1 allocation.
Interim Analysis	After at least 10 evaluable subjects become available in each expansion cohort, futility analyses will be performed. After that, interim analysis may be conducted after every 5 evaluable subjects become available. Phase I interim analyses may also be undertaken for each expansion cohort after the last subject enrolled in the cohort has been followed for 6 months or has progressed, died, or withdrawn from the study treatment. Enrolment to an individual cohort may be stopped due to futility if the Bayesian posterior probability that the confirmed ORR ≥25% in Cohort 1 (AI failure) or ≥20% in Cohort 2 (CDK4/6 + AI failure) is small (see Tables 1 and 2). Enrolment may also be stopped due to futility if the equivalent of no response is observed in the first 10 enrolled evaluable subjects in that cohort or if fewer than 2 confirmed responses are observed in the first 14 and 19 evaluable subjects in Cohort 1 and Cohort 2, respectively. Decision-making criteria for futility are presented in Table 9 for Cohort 1 (AI failure) and Table 10 for Cohort 2 (CDK4/6 + AI failure) in Section 9.3.2 of the Protocol.
Final Analysis	The study will be considered complete for purposes of a final analysis when approximately 70% of all enrolled subjects have died.

Overview of Study Design and Key Features	
Study Status	The totality of Phase I data assessed at the interim analysis does not support continuing investigation of GSK525762 (molibresib) in combination with fulvestrant for the treatment of HR+/HER2- advanced or metastatic breast cancer patients. As interim data failed to demonstrate meaningful clinical benefit in this patient population, enrolment into the study is now closed and the study will not incorporate Phase II. With the implementation of Amendment 06, specific assessments and collection of survival follow-up data will no longer be required. The study will conclude when the last subject has completed/discontinued study treatment and completed the end of treatment visit.

2.4. Statistical Hypotheses / Statistical Analyses

2.4.1. Dose Escalation Phase

Dose escalation decisions will be based on the totality of clinical safety assessment data, as well as PK data. All analyses will be descriptive in nature.

2.4.2. Dose Expansion Phase

For evaluation of efficacy in Cohort 1 (AI Failure) in Phase I, the primary goal is to demonstrate a clinically meaningful response rate, defined as an ORR (equal to CR rate + PR rate) of 25% relative to a 10% response rate suggesting no activity. This will be achieved by testing the null hypothesis of $P0 \leq 0.1$ versus the alternative of $P1 > 0.25$, assuming the maximum response rate for an ineffective drug is 10% and the minimum response rate for an effective drug is 25%.

For evaluation of efficacy in Cohort 2 (CDK4/6 + AI Failure) in Phase I, the primary goal is to demonstrate a clinically meaningful response rate in subjects with measurable disease only. In this cohort, a meaningful response rate is defined as an ORR of 20% relative to a 5% response rate suggesting no activity. This will be achieved by testing the null hypothesis of $P0 \leq 0.05$ versus the alternative of $P1 > 0.20$, assuming the maximum response rate for an ineffective drug is 5% and the minimum response rate for an effective drug is 20%.

Bayesian statistics will be employed to calculate the posterior probability that the ORR ≥25% and ≥10% for Cohort 1 (AI Failure) and ≥20% and ≥5% for Cohort 2 (CDK4/6+AI Failure) at interim assuming a Beta prior for the Binomial distributed data. A weak prior Beta (0.0125, 0.0875) for Cohort 1 and (0.005, 0.095) for Cohort 2 will be used, which is equivalent to the information present in 0.1 subjects.

3. PLANNED ANALYSES

3.1. Interim Analyses

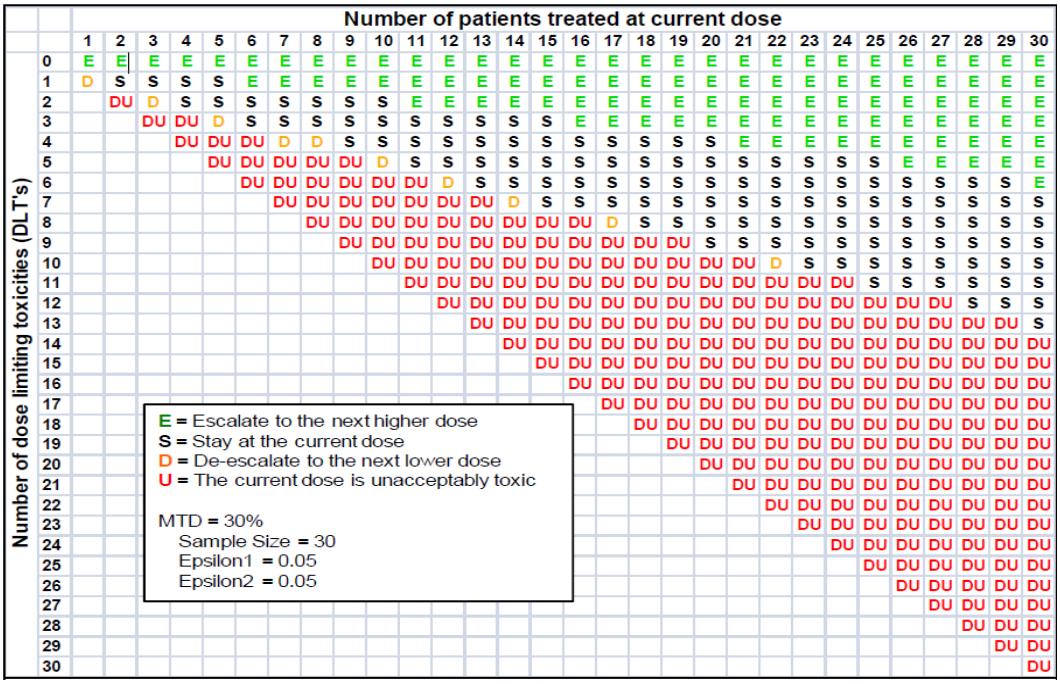
3.1.1. Dose Escalation Phase

No formal interim analysis will be performed for dose escalation decisions in Phase I. These decisions instead will be based primarily on ongoing data review using Spotfire visualization, with additional outputs created by Statistics and Programming if necessary. The assessments driving dose escalation decisions will focus on the safety and tolerability of GSK525762 combined with fulvestrant within each combination of dose level x cohort. Descriptive analyses will be based on the All Treated Population (defined in Section 4, Analysis Populations).

The mTPI design rules, together with predicted dose-limiting toxicity rates at all dose levels, will support the determination of whether to move forward with dose escalation and expansion as planned for Phase I. The mTPI design rests on the assumptions that (a) approximately 30 subjects will complete the DLT evaluation period and (b) the true underlying toxicity rate for GSK525762 in combination with fulvestrant falls within the range of 25% to 35%, centred at 30%.

The monitoring rules guiding dose escalation are provided in Figure 1, below. Columns provide the numbers of subjects treated at the current dose level, while rows provide the corresponding numbers of subjects experiencing toxicity. Entries within the table represent the dose-finding decisions of 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, then the highest dose level is below MTD and the next subject(s) will be treated at the same dose level. In addition, decision U indicates that the current dose level is of unacceptably high toxicity and should be subsequently excluded from the trial. For example, when one of three subject experiences toxicity, the decision is located at row 1/column 3, which is to stay at current dose level (S). Consequently, the next cohort of subjects will be treated at the same dose level currently being used. If none of three subjects experience toxicity, the decision is shown at row 0/column 3, which is to escalate (E) to a higher dose (if available) or to otherwise stop dose escalation when 6 evaluable subjects have been treated at the current dose. Thus, the next cohort of subjects may be treated at the next higher dose level. If three of three subjects experience toxicity, the decision is to de-escalate (DU) to the next lower dose level and subsequently 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



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.

3.1.1.1. Displays to be Created for Dose Escalation Review

Review of preliminary data will be performed after 3-10 evaluable 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 will be able to view subject-level data. In addition to the review of Spotfire data visualisations, summary displays may be provided by Statistics and Programming, as necessary.

GSK has in place a comprehensive and robust review process of all data. During the dose expansion cohorts, all safety, efficacy, and PK data emerging from the study will be reviewed by a Joint Team comprised of participating investigators and study coordinators, together with staff involved in the conduct of the study (i.e. Medical Monitor, Program Lead Physician, Safety (Pharmacovigilance) Physician, Clinical Pharmacokineticist, Statistician, and Clinical Scientist).

Furthermore, multiple review points and mechanisms will be implemented to safeguard subject safety during the conduct of Phase I. The key elements of such safety reviews will include regularly scheduled data reviews and investigator meetings, specific safety

review meetings, and a comprehensive dose selection meeting to be held at the end of Phase I.

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

The GSK study team, in collaboration with study investigators, will review all relevant data (as well as the results of any exploratory analyses) to determine whether the current dose showed acceptable toxicity and to decide the next dose level to be administered based on the totality of the data.

3.1.2. Dose Expansion Phase

3.1.2.1. Interim Futility Analysis

Interim data will be evaluated to monitor efficacy and safety, and a planned interim analysis will be performed when at least 10 evaluable subjects have been enrolled into each of the expansion cohorts at each DL. Enrolment may be stopped early in any of the expansion cohorts for toxicity or lack of efficacy. The decision criteria for early stopping for futility is based on the Bayesian Hierarchical model described below. The decision will be made for each individual prior treatment history-specific cohort.

For the futility interim analyses in each cohort, the enrolment for that cohort may be stopped due to futility if the posterior probability that the confirmed ORR ≥25% or ORR ≥20% in Cohort 1 and Cohort 2, respectively, is small (e.g., less than a 4% chance for a total sample size of 35 subjects). Enrolment may also be stopped due to futility if the equivalent of no objective response (i.e., no confirmed CR or PR) is observed in the first 10 evaluable subjects in that cohort or if fewer than 2 objective responses are observed in the first 14 and 19 evaluable subjects in Cohort 1 and Cohort 2, respectively. An evaluable subject is defined as a subject who has progressed, died, or withdrawn from the study treatment, or is still undergoing treatment and has completed at least two post-baseline disease assessments. For example, if 14 evaluable subjects show only one response at the time of interim analysis, then the cohort may be stopped for futility. Otherwise, enrolment within the respective cohort will continue to the target sample size.

Futility interim analysis decision rules for the 10th through 34th evaluable subject in Cohort 1 (AI Failure) and 10th through 31st evaluable subject in Cohort 2 (CDK4/6 + AI Failure) are presented in Tables 1 and 2, respectively. These rules, which are intended to function as guidelines, specify the number of objective responses (i.e., confirmed CRs or PRs) required to continue enrolment (vs. stop for futility) when the total target sample sizes are up to 35 in Cohort 1 and 32 in Cohort 2. Importantly, actual decisions will depend on the totality of the data.

Table 1 – Decision Making Criteria for Assessing Futility in Cohort 1 (AI Failure)

Number of Evaluable Subjects	≤ This Number of Confirmed Responses to Stop Early for Futility	Probability of continuing enrolling when ORR=0.1	Probability of continuing enrolling when ORR=0.25
10	0	0.6513	0.9437
11	0	0.6513	0.9437
12	0	0.6513	0.9437
13	0	0.6513	0.9437
14	1	0.3971	0.8843
15	1	0.3971	0.8843
16	1	0.3971	0.8843
17	1	0.3971	0.8843
18	1	0.3971	0.8843
19	1	0.3971	0.8843
20	1	0.3971	0.8843
21	2	0.2938	0.8674
22	2	0.2938	0.8674
23	2	0.2938	0.8674
24	2	0.2938	0.8674
25	2	0.2938	0.8674
26	2	0.2938	0.8674
27	3	0.2108	0.8511
28	3	0.2108	0.8511
29	3	0.2108	0.8511
30	3	0.2108	0.8511
31	3	0.2108	0.8511
32	4	0.1509	0.8369
33	4	0.1509	0.8369
34	4	0.1509	0.8369

Table 2 – Decision Making Criteria for Assessing Futility in Cohort 2 (CDK4/6 + AI Failure)

Number of Evaluable Subjects	≤ This Number of Confirmed Responses to Stop Early for Futility	Probability of continuing enrolling when ORR=0.05	Probability of continuing enrolling when ORR=0.2
10	0	0.4013	0.8926
11	0	0.4013	0.8926
12	0	0.4013	0.8926
13	0	0.4013	0.8926
14	0	0.4013	0.8926
15	0	0.4013	0.8926
16	0	0.4013	0.8926
17	0	0.4013	0.8926
18	0	0.4013	0.8926
19	1	0.2027	0.8566
20	1	0.2027	0.8566
21	1	0.2027	0.8566
22	1	0.2027	0.8566
23	1	0.2027	0.8566
24	1	0.2027	0.8566
25	1	0.2027	0.8566
26	1	0.2027	0.8566
27	2	0.1090	0.8362
28	2	0.1090	0.8362
29	2	0.1090	0.8362
30	2	0.1090	0.8362
31	2	0.1090	0.8362

3.1.2.2. Interim Efficacy Analyses

Interim efficacy analyses may also be performed for each expansion cohort after the last subject enrolled in the cohort has been followed for 6 months or has progressed, died, or withdrawn from the study treatment.

3.1.2.3. Displays to be Created for Dose Expansion Review

The All Evaluable Population (see Section 4, Analysis Populations) will be used for futility analyses. As subjects enrol at different times, not all subjects may be on study long enough to undergo multiple or even single post-baseline disease assessment(s). An evaluable subject is a subject who has progressed, died, or withdrawn from the study treatment, or is still undergoing treatment and has completed at least two post-baseline disease assessments.

The All Treated Population (see Section 4, Analysis Populations) will be used to produce study population, efficacy (other than futility), and safety summaries.

The ORR is defined as the percentage of subjects in the population who show a best overall response (BOR) of confirmed CR or PR per RECIST v1.1. The ORR will be provided with its exact 95% confidence interval (CI). 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).

A listing of subject status and BOR will be provided. This listing will be sorted by date of the subject's first dose and will show whether each subject is still undergoing study treatment, whether the subject has had at least two post-baseline radiological disease assessments, whether the subject is considered evaluable for the futility analysis, and the subject's BOR (including confirmed and unconfirmed response).

Summaries, as well as data listings, of AEs, drug related AEs, AEs leading to study treatment discontinuation and other dose modifications, SAEs, fatal SAEs, study treatment related SAEs, exposure to GSK525762 and fulvestrant, and GSK525762 and fulvestrant dose modification(s) will be provided. In addition, summaries of laboratory assessments, vital signs, ECGs, Eastern Cooperative Oncology Group (ECOG) scores, and left ventricular ejection fraction (LVEF) results will be provided.

PK analysis will be performed using the PK Population (as defined in Section 4, Analysis Populations), with results presented by subgroups representing combinations of dose level x cohort, for GSK525762, its relevant metabolites, and fulvestrant (see Section 5.5.2 for subgroup descriptions). For further evaluation of the PK of GSK525762, the results within this study may also be compared to the results of other studies, wherein higher dose level(s) were administered.

Refer to Appendix 11: List of Data Displays for the full list of displays.

3.2. Final Analysis

The final analysis will be performed when approximately 70% of all enrolled subjects have died. Also, the final analysis will occur after all required database cleaning activities have been completed and both final database release (DBR) and database freeze (DBF) have been declared by Data Management.

As the study and project have been terminated, the primary analysis will occur once the termination decision has been confirmed, and the final analysis will occur once all ongoing subjects have completed the study.

As final analysis may be performed when some subjects are still in follow-up and additional data may be available by study closure, an amendement to this RAP may be performed, if needed for guiding 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 • Enrolled subjects
All Treated Population	Subjects who receive at least one dose of study treatment (GSK525762 or fulvestrant). In addition to primary analyses of study population, safety, and efficacy, this population will be used for decision-making during dose escalation.	• Study population • Anti-cancer activity • Safety
Modified All Treated Population	All subjects who receive at least one dose of GSK525762 and fulvestrant.	• Efficacy • Safety (if different from the All Treated population)
All Evaluable Population	Subjects who have at least two post-baseline radiological disease assessments or have progressed or died or permanently withdrawn from the study treatment. This population will be used for decision-making at the interim futility analysis.	• Dose escalation phase • Interim futility analyses
PK Population	Subjects from the All Treated Population for whom a PK sample is obtained and analysed.	• PK analysis

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

4.1. Protocol Deviations

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

Protocol deviations will be tracked by the study team throughout the study in accordance with the Protocol Deviation Specifications developed by PAREXEL. To ensure that all important deviations are captured and categorised in the protocol deviations dataset, data will be reviewed prior to DBF at the end of Phase I. This dataset will be the basis for all summaries and listings of protocol deviations, including a separate summary and separate listing dedicated to all deviations related to inclusion/exclusion criteria. These latter data displays will be based on data recorded on the inclusion/exclusion electronic case report form (eCRF).

As no Per Protocol Population has been defined for this study, protocol deviations will not be used to determine membership in any particular analysis population.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Data will be summarised and listed according to GSK reporting standards, as applicable. Summaries and listings will be displayed by or will otherwise incorporate the subgroups described below and in Section 5.5.2, Examination of Subgroups.

5.1. Study Treatment and Sub-group Display Descriptors

Data will be summarised and listed according to GSK reporting standards, as applicable. All data displays (tables, figures, and 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 study treatment dose level. Actual dose levels will depend on outcomes of the dose escalation phase but will follow the same format. Subgroups described in Section 5.5.2, Examination of Subgroups, may also be used in summaries.

Treatment Description	Treatment Label / Column Header	Order[1]
GSK525762 60mg + fulvestrant 500 mg	GSK762 60 mg + FUL 500 mg	1
GSK525762 80mg + fulvestrant 500 mg	GSK762 80 mg + FUL 500 mg	2
Fulvestrant 500 mg	Fulvestrant 500 mg [2]	3
GSK525762 60mg	GSK762 60 mg [2]	4
GSK525762 80mg	GSK762 80 mg [2]	5

NOTES:
1. Order represents treatments being presented in TFL, as appropriate.
2. Required only for tables that are displayed separately for individual treatment.

Sub-Group Descriptions			
Interactive response technology (IRT)		**Data Displays for Reporting**	
Code	**Description**	**Description [1]**	**Order [2]**
A	DL1_COHORT1	GSK762 60 mg + FUL 500mg (AI Failure)	1
A	DL1_COHORT2	GSK762 60 mg + FUL 500mg (CDK4/6 + AI Failure < 12M)	2
A	DL1_COHORT2	GSK762 60 mg + FUL 500mg (CDK4/6 + AI Failure >= 12M)	3

Sub-Group Descriptions			
Interactive response technology (IRT)		**Data Displays for Reporting**	
Code	**Description**	**Description [1]**	**Order [2]**
A	DL1_COHORT2	GSK762 60 mg + FUL 500mg (CDK4/6 + AI Failure >= 12M Bone Only Disease)	4
B	DL2_COHORT1	GSK762 80 mg + FUL 500mg (AI Failure)	5
B	DL2_COHORT2	GSK762 80 mg + FUL 500mg (CDK4/6 + AI Failure)	6

NOTES:
1. The duration of 12 months equals, on average, 365.25 days.
2. Order represents the order of treatments as presented in each TFL display.

5.2. Reporting Conventions

- Unless otherwise specified, the denominator used in the calculation of percentages will be based on the number of subjects with non-missing values for the given scheduled visit and assessment or parameter.
- All data are reported according to the dose/regimen initially received by the subject.
- At 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 mean/median plots. Listings of PK concentration-time data will be displayed 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.
- Programmers should refer to GSK IDSL standards (as applicable) for decimal place conventions and expand if necessary. Unless stated otherwise, descriptive summaries will include n, mean, standard deviation (SD), median, minimum, and maximum for continuous variables and n and percentage for categorical variables. Minimum and maximum values will be displayed with the same precision as original source data, mean and median values will be displayed with one additional decimal place, and SD values will be displayed with two additional decimal places.

- This is a multicentre study. Data from all study centres will be integrated into derivations and summaries without controlling for centre effects.
- Analyses will be performed using SAS statistical software version 9.4 or later. Programs will be imported into HARP, and the final outputs will be produced by running drivers in HARP. Some graphics may be produced using Tibco Spotfire Clinical Graphics, comprising S-Plus (R) version 7.0.6 or later.
- Deviations from any planned analyses in this RAP will be identified in the final CSR.

5.3. Baseline and Post-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 do not receive the study treatment, baseline will be defined as the latest 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 are missing, then no derivations (e.g., change from baseline) will be performed and baseline will be set to missing.

5.3.1. Change from baseline

Following the initiation of treatment, absolute change from baseline will be calculated as: post-baseline value – baseline value.

Percent (i.e., relative) change from baseline will be calculated as: (absolute change from baseline value ÷ baseline value) x 100.

If either the baseline value or post-baseline value is missing, then both the absolute and relative changes from baseline will be set to missing.

5.3.2. Multiple Assessments

All data will be reported as corresponding to a nominal visit, as no visit windows will be applied during dataset creation. Data from unscheduled visits will be included in summaries reporting worst-case post-baseline results only and in all relevant data listings.

For summaries in which data are collapsed across multiple planned time intervals, the means of intervals will be summarised.

With the exceptions of ECG and echocardiogram (ECHO) or multiple gated acquisition (MUGA) assessments, if multiple assessments of the same type are performed on different days but reported for the same scheduled assessment, then only the worst-case assessment results for that scheduled assessment will be analysed.

With the exceptions of laboratory, ECG, and ECHO/MUGA assessments, the reporting of multiple assessments of the same type on the same date for the same visit or timepoint will be addressed by using the mean of the multiple reported measurements within analyses.

For laboratory assessments, data may be collected from both local and central laboratories for the same visit or timepoint, but, in such case, only data from the central laboratory will be analysed to maintain comparability across measurements and subjects.

For ECG and ECHO/MUGA assessments, both local investigator and central cardiologist readings will be performed for each visit/timepoint. For these assessments, only post-baseline data collected using the same method (i.e., ECG, ECHO vs. MUGA) and by the same source (i.e., local vs. central cardiologist read) as the baseline assessment will be used to derive change from baseline.

Data from all assessments, regardless of whether scheduled or unscheduled and performed singly or in multiple, will be included in the data 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 Covariates, Other Strata, and 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 (a) the study phases (Phase I vs. Phase II), (b) the combinations of dose level (e.g., DL-1, DL1, DL2) and cohort (Cohort 1 [AI Failure] vs. Cohort 2 [CDK4/6 + AI Failure]), and (c) the combinations of dose level, prior treatment, timing of a progressive disease response to prior treatment, and evidence of bone-only disease (see Section 5.1, Study Treatment and Sub-group Display Descriptors, for descriptions).

5.6. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined across multiple 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
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

Study population analyses will be based on the All Treated Population, unless otherwise specified. Analyses will include descriptive summaries and data listings of subject disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and treatment exposure, based on GSK Core Data Standards. Details of all planned displays are presented in Appendix 11: List of Data Displays.

6.2. Disposition of Subjects

Using the All Screened Population, the numbers and percentages of subjects in each analysis population (described in Section 4, Analysis Populations) will be summarised. A listing of subjects excluded from the analysis populations and both a summary and a listing of subject screening status and reasons for screen failure will 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 that they are displayed on the eCRF. A listing of study treatment discontinuation will be generated. The listing will include last dose date, reasons for study treatment discontinuation, and study phase of 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 either are ongoing or withdrew from the study. Primary reasons for study withdrawal will also be summarised. 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 categorization) will be included in a listing. A separate listing dedicated to deviations related to inclusion/exclusion criteria will also be provided. 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, and weight will be summarised as continuous variables, whereas sex, race, and ethnicity will be summarised as categorical variables. Age will be additionally summarised as a categorical variable using the EudraCT categories of 18-64, 65-84 and ≥85 years and GSK IDSL categories of ≤18, 18-65, 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.

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.

Disease characteristics at initial diagnosis and study screening will be summarised separately and provided in separate listings. As appropriate per summary, characteristics may include primary tumor type, stage, lesion status, time since initial diagnosis, and time since latest disease progression. Sites of metastatic disease at screening will be both summarised and included in a listing, and, lastly, a summary describing disease burden at baseline will be provided.

Anti-cancer therapy will be coded using the GSK drug coding dictionary. Separate summaries will be produced for prior anti-cancer therapy (dedicated to all therapies, including radiotherapies), prior dictionary-coded therapy, and number of therapy regimens. The details of prior and subsequent anti-cancer therapies will be disclosed in two listings, one for all therapies and one for radiotherapies. A summary of best response to the most recent prior anti-cancer therapy will also be provided.

Prior and on-treatment cancer-related surgical procedures will be summarized separately but included in the same listing.

6.5. Concomitant Medications

Concomitant medications, coded using the GSK drug coding dictionary, will be both summarised and included in a listing. 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 will be counted once per 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

Efficacy analyses will be based on the Modified All Treated Population, unless otherwise specified. The results of all efficacy analyses will be presented by subject subgroup, defined by the combination of dose level, prior treatment, timing of a progressive disease response to prior treatment, and evidence of bone-only disease (see Section 5.5.2, Examination of Subgroups).

7.1. Endpoints / Variables

Best Overall Response (BOR)

BOR is defined as the best confirmed or unconfirmed response observed following the initiation of treatment through first documentation of progressive disease (PD) or initiation of new anti-cancer therapy, whichever occurs earlier. Responses following the onset of treatment will be assessed by the investigator per RECIST v1.1 criteria and, listed from best to worst, may include: CR, PR, SD (or non-CR/non-PD), PD, and not evaluable (NE).

Objective Response Rate (ORR)

ORR is defined as the percentage of subjects in the population who demonstrate a BOR of confirmed CR or PR, as assessed by the investigator per RECIST v1.1 criteria.

Disease Control Rate (DCR)

DCR is defined as the percentage of subjects in the population with a confirmed CR, confirmed PR, or SD lasting ≥6 months, as assessed by the investigator per RECIST v1.1 criteria.

Duration of Response (DoR)

DoR is defined as the time (in months) from date of first documented evidence of confirmed CR or PR to the date of first documented PD, as assessed by the investigator per RECIST v1.1 criteria, or to the date of death due to any cause among subjects with a BOR of confirmed CR or PR. Subjects who have not shown disease progression or died at the time of analysis will be considered censored as of the date of their last evaluable disease assessment. Censoring rules will follow those for PFS, specified in Table 3.

Progression-Free Survival (PFS)

PFS is defined as the time (in months) from the date of first dose until the date of first documented PD, as assessed by the investigator per RECIST v1.1 criteria, or date of death due to any cause, whichever occurs first. Subjects who have not shown disease progression or died at the time of analysis will be considered censored as of the date of

their last evaluable disease assessment. Rules for determining the dates of PFS events and censoring are described in Table 3.

Table 3 – Assignments of Progression and Censoring Dates for PFS Analysis

Scenario	Date of Event (PD and/or Death) or Censored	Event (PD and/or Death) or Censored
No adequate baseline assessments[1] and subject has not progressed or died (if the subject has progressed/died, follow the rules for death indicated at the bottom of the table). Note that PD may be documented in the RS (Response) or DS (Disposition) dataset.	First dose	Censored
No post-baseline assessments and subject has not died (if the subject has died, follow the rules for death indicated at the bottom of the table) and subject has no documented PD in DS dataset.	First dose	Censored
PD/death documented before any new anti-cancer therapy is received. Note that this includes PD/death at baseline or without adequate assessments.	Date of assessment of PD[2] or date of death, whichever occurs first	Event
With post-baseline assessment(s) but no documented PD/death or new anti-cancer therapy.	Date of last 'adequate' assessment of response[1]	Censored
No adequate post-baseline assessment before start of new anti-cancer therapy and no PD documented in DS dataset.	First dose	Censored
With adequate post-baseline assessment(s) and new anti-cancer therapy started but without PD documented[3]	Date of last 'adequate' assessment of response[1] (prior to starting new anti-cancer therapy)	Censored
Death or PD documented in RS or DS dataset (without prior or new anti-cancer therapy) after two or more missed consecutive scheduled assessments	Date of last 'adequate' assessment of response[1] (prior to missed assessments) or date of first dose without 'adequate' assessment[1,4]	Censored

[1] An adequate assessment is defined as a scheduled or unscheduled assessment in which the Investigator determines a disease response of CR, PR, or SD.

[2] Equals the earliest of (a) date of radiological assessment showing new lesion (if progression is based on new lesion), or (b) date of radiological assessment showing unequivocal progression in non-target lesions,

or (c) date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions).

[3] If documentation of PD and start of new anti-cancer therapy occur on the same day, PD will be assumed to have occurred first (i.e., prior to new therapy), with PD reported as the outcome and the assessment date reported as the event date.

[4] Relevant if the previous assessment is (a) earlier than Day 274 and the difference between PD/death and last adequate assessment is >126 days, or (b) between Day 274 and Day 344 and the difference between PD/death and last adequate assessment is >154 days, or (c) after Day 344 and the difference between PD/death and last adequate assessment is >182 days. Note that scheduled disease assessment window is +/- 7 days.

7.2. Summary Measures

Objective Response Rate (ORR)

The number and percentage (representing ORR) of subjects in the population who show a BOR of confirmed CR or PR will be presented with exact 95% CI for ORR. Subjects with unknown or missing responses will be considered to be non-responders (i.e., subjects will be included in the denominator when calculating percentage). A spider plot of percent change from baseline in target lesions over time per subject and a waterfall plot of maximum percent reduction from baseline in tumour measurement per subject will be provided.

Disease Control Rate (DCR)

The number and percentage (representing DCR) of subjects in the population who show a BOR of confirmed CR, confirmed PR, or SD lasting ≥6 months will be presented with exact 95% CI for DCR. Subjects with unknown or missing responses will be treated as non-responders (i.e., subjects will be included in the denominator when calculating percentage).

Duration of Response (DoR)

Given a sufficient number of responses, DoR will be summarised using the Kaplan-Meier method. The median and 25th and 75th percentiles of DoR will also be estimated, with their corresponding 95% CIs estimated using the Brookmeyer-Crowley method (1982).

Progression-Free Survival (PFS)

PFS will be estimated using the Kaplan-Meier method. The median and 25th and 75th percentiles of PFS will also be estimated, with their corresponding 95% CIs estimated using the Brookmeyer-Crowley method (1982). A Kaplan Meier curve may also be produced, if the data warrant.

7.3. Population of Interest

Efficacy analyses will be based on the Modified All Treated Population, unless otherwise specified.

7.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: 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 will be summarised using descriptive statistics, graphically presented (if appropriate), and listed.

Primary Statistical Analyses	
Endpoint(s)	**Method of Analysis**
ORR	Percentage, Exact 95% CI
Secondary Statistical Analyses	
Endpoint(s)	**Method of Analysis**
DCR	Percentage, Exact 95% CI
DoR	Kaplan-Meier median and 25th and 75th percentiles, Brookmeyer-Crowley 95% CIs (if data warrant)
PFS	Kaplan-Meier median and 25th and 75th percentiles, Brookmeyer-Crowley 95% CIs (if data warrant)

8. SAFETY ANALYSES

Safety analyses will be based on the All Treated Population, unless otherwise specified. The results of all safety analyses will be presented by subject subgroup, defined by the combination of dose level, prior treatment, timing of a progressive disease response to prior treatment, and evidence of bone-only disease (see Section 5.5.2, Examination of Subgroups).

8.1. Adverse Events Analyses

Analyses of AEs, including summaries of all AEs, SAEs, and other significant AEs, will be based on GSK Core Data Standards. Moreover, all analyses will be performed on treatment-emergent AEs (TEAEs) only (see Section 15.4.3 for definition). The details of the planned displays are provided in Appendix 11: List of Data Displays.

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

Several summaries of AEs will be produced, including counts and percentages of subjects with:

- Any AE.
- Non-serious AEs.
- AEs related to study treatment (any, GSK525762, fulvestrant).
- AEs of Grade 3-4.

- Grade 3-4 AEs related to study treatment (any, GSK525762, fulvestrant).
- AEs leading to permanent discontinuation of study treatment (any, GSK525762, fulvestrant).
- AE leading to dose reductions of study treatment (any, GSK525762, fulvestrant).
- AEs leading to dose interruptions/delays of study treatment (any, GSK525762, fulvestrant).
- SAEs.
- SAEs related to study treatment (any, GSK525762, fulvestrant).
- Non-fatal SAEs related to study treatment (any, GSK525762, fulvestrant).
- Dose-limiting toxicities.

A summary of common non-serious AEs (those that occur in ≥5% of subjects) will be provided (no rounding for the percentage will be used in terms of 5% threshold; e.g., events with 4.9% incidence rate will not be included in this table). This summary will contain the numbers and percentages of subjects per common non-serious adverse event. This summary table and those bulleted above will be displayed by SOC and PT.

A summary of the numbers and percentages of subjects with any AEs by maximum grade will be produced. At the subject level, a conservative approach will be taken to compute the maximum grade of AEs. Specifically, when grade is missing for one or more AEs for a single subject, the subject's maximum grade will be considered unknown. AEs will be sorted by MedDRA PT in descending order of total incidence. The summary will use the following algorithms for counting the subject:

- PT row: Subjects who experience multiple AEs of the same PT but with different grades will only be counted once with the maximum grade.
- Any event row: Each subject with at least one AE will be counted only once at the maximum grade no matter how many events they have.

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

Separate summaries will be provided for study treatment-related AEs, including GSK525762-related, fulvestrant-related, and any treatment-related (i.e., GSK525762 or fulvestrant-related) AEs. 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. That is, 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. A summary of study treatment-related AEs by maximum grade will also be provided.

A summary of the number of subjects who experience DLTs will be provided. Lastly, all AEs, including DLTs, will be described in subject-level data listings.

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 AESIs are not defined in the protocol but are noted in the Investigational Brochure. Changes to the MedDRA dictionary may occur between the start of the study and time of reporting, and emerging data from on-going studies may highlight additional AESIs. Therefore, the specific AESIs to be studied and the list of terms to be used per AESI will be based on Safety Review Team agreements that are in place at the time of database lock. Details of the planned displays are provided in Appendix 11: List of Data Displays.

AESIs will include, but may not be limited to, the following categories:

- Haematopoietic thrombocytopenia, Standardised MedDRA Query (SMQ)
- Haemorrhages [excluding 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 Preferred Terms

The PTs for AESIs will be provided by the GSK525762 Pharma Safety representative before DBR, based on the most up-to-date MedDRA version.

The number and percentage of subjects with AESIs will be summarised by AESI category, PT, and maximum toxicity grade in one table. A summary and a listing of event characteristics for each AESI category will also be provided, including number of subjects with any event, number of events, number of subjects with any serious event, number of subjects with any study treatment-related event, outcome of the event, maximum grade, and action taken for the event. The percentage of subjects with an AESI will be calculated using the total number of subjects as the denominator. The percentages of subjects associated with individual event characteristics will be calculated using the number of subjects with any AESI as the denominator. At a subject level, a worst-case approach will be applied for determining event outcome and maximum grade. That is, a subject with multiple AESIs will be counted only once based on the worst case from all AESIs experienced by the subject. For action taken to an event, subjects will be counted once per action. For example, if a subject has an event leading to both reduction of the study treatment dose and discontinuation of the study treatment, the subject will be counted once under both actions.

For each category of AESI, a summary of time to onset (in days) and duration of first occurrence (in days) will be provided, with each analysed as both a continuous and a categorical variable. Time to onset will be summarised within categories of 1-14 days, 15-28 days, and >28 days, and duration of first occurrence will be summarised within categories of 1-5 days, 6-10 days, and >10 days.

8.3. Deaths and Serious Adverse Events

For any subject who withdraws consent, no data after the date of consent withdrawal from this subject, including death, should 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 in the population. Within this summary, subjects will be classified by time of death relative to last dose of medication (>30 days vs. ≤30 days) and primary cause of death (disease under study, SAE related to study treatment, or other). A subject-level data listing will be generated to disclose the details of all death events.

All SAEs will be tabulated based on the number and percentage of subjects from the population who experience the specific SAE. Multiple summary tables will be generated, with statistics displayed in descending order of total incidence per 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 relatedness data. That is, summary tables will include events with the relationship to study treatment as "Yes" or missing.

SAEs will be 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 subjects with:

- AEs leading to permanent discontinuation of study treatment (any, GSK525762, or fulvestrant).
- AEs leading to dose interruptions/delays of study treatment (any, GSK525762, or fulvestrant).
- AEs leading to dose reductions of study treatment (any, GSK525762, or fulvestrant).

8.5. Extent of Exposure

Details of the extent of exposure to GSK525762 and fulvestrant will be both summarised and listed separately.

GSK525762:

The duration of exposure to study treatment in months (from first day of treatment to end of treatment in Phase I) will be summarised. Descriptive statistics, including mean, median, standard deviation, minimum, and maximum, will be computed for duration of study treatment. In addition, treatment duration will be summarised within the following categories: <3 months, 3 months to <6 months, 6 months to <12 months, and ≥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 number and percentage within categories of reason for reduction. Dose interruptions/delays will be summarised by number of interruptions/delays, reasons for interruption/delay, and duration of interruption/delay (in days). Descriptive statistics, including mean, standard deviation, median, minimum, and maximum, will be computed for interruption/delay duration, and the number and percentage of subjects within the interruption/delay duration categories of <7, 7-14, and >14 days will also be computed. A summary of dose escalation will also be provided, if applicable. All dose modifications (reductions, interruptions/delays, and escalations) will be listed separately.

Fulvestrant:

Duration of exposure, as well as cumulative dose and dose intensity (defined in Section 15.6.3), will be summarised for fulvestrant using descriptive statistics for a continuous variable.

Dose reductions will be summarised by number of reductions and number and percentage within categories of reason for reduction. Dose delays will be summarised by number of delays, number and percentage within categories of reason for delay, and duration of delay (in days). Descriptive statistics, including mean, standard deviation, median, minimum, and maximum, will be computed for delay duration. Missed doses will be summarised by number of missed doses and number and percentage within categories of reason for missed dose.

These summaries of dose modifications will be provided only if the data warrant. All dose reductions, interruptions/delays, and missed doses will be listed separately.

8.6. Pregnancies

Details of all pregnancies will be collected after the start of study treatment and until at least 90 days post-last dose of study drug. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE. If a subject should become pregnant while on study, then information describing the pregnancy will be included in the narratives, and no separate table or listing will be produced.

8.7. Clinical Laboratory Analyses

Laboratory tests, including clinical chemistry, haematology, urinalysis, and liver function tests, will be based on GSK Core Data Standards. Details of the corresponding planned displays can be found in Appendix 11: List of Data Displays. Laboratory tests performed for the assessment of toxicity will include the following:

Figure 2 – Clinical Laboratory Tests

Clinical Chemistry
Sodium
Fasting Glucose
Potassium
Magnesium
Chloride
Calcium (total and ionized)
Total Carbon Dioxide
Total Protein
Blood Urea Nitrogen
Albumin
Creatinine
Hematology
White Blood cell count
Hemoglobin
Platelet count
Automated White Blood Cell Differential:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils
Liver Function
Bilirubin (Total and, if Total is abnormal, then Direct needed)
Aspartate Aminotransferase (AST)
Alanine Aminotransferase (ALT)
Alkaline Phosphatase
Urinalysis
Specific gravity
pH
Glucose
Protein
Blood
Ketones
Microscopic examination (if urinalysis is abnormal)
Cardiac
Troponin (I or T), may be collected at central laboratory if local draw is not possible
N-terminal pro b-type natriuretic peptide (NT-proBNP)
Fasting Lipid Panel (Total Cholesterol, LDL, HDL, Triglycerides)
Other
Coagulation:
Prothrombin Time/Internal Normalized Ratio (INR)
Partial Thromboplastin Time (or Activated Partial Thromboplastin Time [aPTT])
Fibrinogen
Factor VII Assay
Endocrine:
Thyroid Stimulating Hormone (TSH)
Free Thyroxine 3 (Free T3)

Free Thyroxine 4 (Free T4)
Hemoglobin A1c
FSH (for pre- and peri-menopausal subjects only)
Estradiol (for pre- and peri-menopausal subjects only)
Safety Screening:
HIV
HbSag
HCV antibody
Pancreatic Markers:
Amylase
Lipase

A summary of laboratory values and derived change-from-baseline values by scheduled visit will be provided, using mean, median, standard deviation, minimum and maximum. Summaries of laboratory data will also be provided by maximum toxicity grade, using reported grades based on NCI-CTCAE v4.0. For any subject, a missing baseline grade will be assumed as grade 0.

Summaries of worst-case grade increase from baseline grade will be provided for all 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.

Summaries will also include grade increase from baseline by scheduled visit. For laboratory tests that are graded for both low and high values, summaries will be generated separately and labeled by direction (e.g., low and high sodium level will be summarised as hyponatremia and hypernatremia, respectively).

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, and coagulation 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, Baseline and Post-Baseline Definitions.

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.

Although all data will be reported according to the nominal visit for which they were recorded (i.e., no visit windows will be applied), summaries by visit will include data from scheduled assessments only. Unscheduled assessment data will be incorporated into "worse-case post-baseline" summaries, which capture the worst case across all scheduled and unscheduled visits following first dose of study treatment.

8.7.1. Analyses of Liver Function Tests

In addition to chemistry laboratory summaries and listings incorporating bilirubin (total and direct), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase results, a summary and a listing of liver monitoring/stopping events defined by liver chemistry will be provided.

A summary and a listing of hepatobiliary laboratory abnormalities, including possible Hy's Law cases, will also be provided. Possible Hy's law cases will be defined as any event of either: (a) ALT ≥3 × the upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or (b) ALT ≥3 × ULN and INR >1.5, if INR is 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.

8.8. Other Safety Analyses

The analyses of non-laboratory safety test results, including those from vital signs, performance status, ECG, and ECHO/MUGA assessments, will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 11: List of Data Displays.

8.8.1. Vital Signs

Raw vital sign values, as well as computed changes 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. These summaries will display the number and percentage of subjects in the population with any grade increase, an increase to grade 2, and an increase to grade 3 at each scheduled visit and at the visit showing the worst-case post-baseline results.

8.8.2. Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status will be summarised at baseline and each post-baseline scheduled visit. Summaries will include the numbers and percentages of subjects in the population at each planned assessment time. A summary of change-from-baseline by scheduled visit will be generated, as will a summary of the worst-case and best-case post-baseline changes during the study (i.e., using categories of improved, no change, and deteriorated). A supporting listing will also be provided.

8.8.3. 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 heart rate and measures PR, QRS, QT and QTcF intervals. The baseline QTcF value will be computed as the mean of the triplicate Week 1 Day 1 pre-dose QTcF results (see Section 5.3, Baseline and Post-Baseline Definitions). 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 with normal, abnormal clinically significant, and abnormal not clinically significant ECG findings will be displayed by scheduled visit, as well as for the worst-case post-baseline assessment.

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 two sources will not be combined.

QTcF prolongation will be monitored throughout the study. QTcF values will be rounded to the integer and 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 in the population with any grade increase, an increase to grade 2, and an increase to grade 3 at each scheduled visit and at the visit showing the worst-case post-baseline results. Missing baseline grade will be assumed as grade 0.

Changes in QTc values will be categorized into ranges of clinical concern, namely differences of 31-60 msec and >60 msec from baseline. A summary of change in QTc value will display the number and percentage of subjects in each range of clinical concern per scheduled visit and at the visit showing the worst-case post-baseline results. Subjects with missing baseline values will be excluded from this summary.

Listings of all ECG results and all abnormal ECG findings will be provided.

8.8.4. LVEF

Both absolute and relative change from baseline in LVEF will be summarised at each scheduled visit and at the visit showing the worst-case post-baseline results. Only the post-baseline assessments that used the same method (ECHO or MUGA) and source (local or central) as the baseline assessments will be used to derive the change from baseline. Absolute change from baseline will be categorized as follows:

- No change or any increase (i.e., increases of 0 to <10%, 10 to <20%, and ≥20%)
- Any decrease (i.e., decreases of >0 to <10%, 10 to <20%, and ≥20%)
- Decrease ≥10% and ≥ lower limit of normal (LLN)
- Decrease ≥10% and < LLN
- Decrease ≥20% and ≥ LLN
- Decrease ≥20% and < LLN

Relative change from baseline will be categorized as follows:

- Decrease ≥20% and ≥ LLN
- Decrease ≥20% and < LLN

A listing of all LVEF results will be produced, including both absolute and relative changes from baseline.

8.8.5. Liver Events

For any liver events that occur during the study, the Roussel Uclaf Causality Assessment Method (RUCAM) score will be derived and incorporated into a listing of data describing liver monitoring/stopping events. The score incorporates whether the subject was age 55 years or older, the subject became pregnant, liver imaging was normal or not, a biopsy was taken or not, fasting or significant dietary change occurred, and the subject took any unconventional medications, as well as the relative timing of the event (i.e., while on treatment vs. after stopping treatment) and computed durations from first dose to start of the liver event and from last dose to start of the liver event.

9. PHARMACOKINETIC ANALYSES

9.1. Primary 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.

Concentrations of GSK525762, active metabolites (GSK3529246), and GSK525762 total active moiety (i.e. GSK525762 + GSK3529246 after conversion from ng/mL to nM concentrations) and fulvestrant 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.

Mean/median plots of concentration (GSK525762 in nM, GSK3529246 in nM, and total active moiety in nM on the same plot) over time will be provided for each analyte using actual elapsed time for Week 1 and Week 3 for GSK525762, GSK3529246, and Total active moiety and using overall duration of the study for fulvestrant.

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

The PK parameters presented in the table below will be derived during programming. This will be the responsibility of the Statistics and Programming group at PAREXEL under the direction of the Clinical Pharmacology Modeling and Simulation (CPMS) Department at GSK.

The parameters will be determined from the concentration-time data for GSK525762 (in ng/mL), active metabolites (GSK3529246 in ng/mL), and total active moiety (i.e. GSK525762 + GSK3529246 in nM), 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 x 1000) + (GSK3529246 concentration in ng/mL / molecular weight of 396 x 1000).

Parameter	Parameter Description
C_{max}	Maximum observed concentration; determined directly from the concentration-time curve.
T_{max}	Time from first administration to occurrence of C_{max}; determined directly from the concentration-time curve.
C_{τ}	Also referred to as "C_{trough}"; observed concentration at the end of a dosing interval, immediately before the next administration; determined directly from the concentration-time curve.

NOTE: Additional parameters may be included as required

9.1.2. Summary Measure

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, and fulvestrant.

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/scheduled visit.

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

The PK parameters described in Section 9.1.1.2 will also be summarised descriptively (using mean, SD, median, minimum, maximum, geometric mean with SD, coefficient of variation [CV], and 95% CI of log-transformed parameters, if applicable), separately for GSK525762, active metabolites (GSK3529246), and the total active moiety of GSK525762.

9.1.3. Population of Interest

The primary PK analyses will be based on the PK Population, unless otherwise specified.

10. PHARMACODYNAMIC ANALYSIS

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 Population, unless otherwise specified. All summaries and data listings will use treatment labels as specified in Section 5.1, Study Treatment and Sub-group Display Descriptors.

Summaries of raw values and absolute change-from-baseline values from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC-QLQ-C30) and Breast-23 (EORTC-QLQ-BR23) scales will be provided in tables. Summaries of raw values and absolute change-from-baseline values from Patient Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) will be provided in tables. Single items from EORTC-QLQ-C30, EORTC-QLQ-BR23, and PRO-CTCAE will be provided in listings.

Baseline will be defined as the visit prior to the start of Week 1 Day 1 dosing. Details of data displays are presented in Appendix 11: List of Data Displays.

12. REFERENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics, 1982; 38:29-41.

Aaronson, N. K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N. J., Takeda, F. (1993). The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. *JNCI: Journal of the National Cancer Institute, 85*(5), 365-376.

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 study in accordance with the Protocol Deviation Specification document.

13.1.1. Exclusions from Per Protocol Population

No Per Protocol Population will be defined or used for this study.

13.2. Appendix 2: Schedule of Activities

Refer to Protocol Section 7, Study Assessments and Procedures.

13.3. Appendix 3: Assessment Windows

No assessment windowing will be applied in this study.

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, ECHO/MUGA scans, ECOG 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
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

NOTES: If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.

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 or Date of Death) – (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 days).
Drug-Related	If relationship is marked 'YES' on Inform/CRF (or if value is missing).

NOTES:

- If completely missing start dates, then the AE will be considered as TEAE.
- If the study treatment stop date is missing, then the AE will be considered to be On-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\mid201973
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):
  ○ 4.03 to 4.23: General Principles
  ○ 5.01 to 5.08: Principles Related to Data Listings
  ○ 6.01 to 6.11: Principles Related to Summary Tables
  ○ 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:

○ Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. ○ 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: ○ Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). ○ 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.
ADPC data file	To create ADPC the SDTM PC domain dataset will be merged with the Subject-Level Analysis Dataset (to get demographic information) and with SDTM EX domain (to get reference timepoint date). Reference timepoint date will be populated for both study drug and active metabolite based on study treatment information from SDTM EX domain. To populate analysis values in ADPC (AVAL(C)) adjustments to the PCSTRESN will be done based on imputation rules from "Non-Compartmental Analysis of Pharmacokinetic Data, CPMS Global" document.

	Total Moiety parameter will be added, along with concentrations of study drug and active metabolite, and derived as the sum of study drug and active metabolite concentrations converted to nM units. 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 x 1000) + (GSK3529246 concentration in ng/mL / molecular weight of 396 x 1000).
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 Parameters to be Derived by PK Programmer	The following PK parameters will be derived by the PK Programmer: C_{max}, T_{max}, and C_{τ}.
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. • Subjects 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 to Reference Date: o If Ref Date = Missing, then Study Day = Missing. o If Ref Date < Study Treatment Start Date, then Study Day = Ref Date – Study Treatment Start Date. o If Ref Data ≥ Study Treatment Start Date, then Study Day = Ref Date – (Study Treatment Start Date) + 1.
Change from Baseline
• Absolute Change from Baseline = Post-Baseline Visit Value – Baseline Value. • Percent (i.e., Relative) Change from Baseline = ([Post-Baseline Visit Value – Baseline Value] ÷ Baseline Value) x 100. If either the Baseline or Post-Baseline Visit Value is missing, then both Absolute and Relative Change from Baseline are 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 showing the response (not to the date on which confirmation ultimately occurs); for other response categories not requiring confirmation (SD [or Non-CR/Non-PD], NE, PD), the date of response is also assigned to the earliest date of disease assessments showing the response.
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 13.7.3.

13.6.2. Study Population

Demographics
Age
• GSK standard 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

13.6.3. Efficacy

Primary Endpoint
Objective Response Rate (ORR)
• Defined as the percentage of subjects in the population who demonstrate a Best Overall Response (BOR) of confirmed Complete Response (CR) or Partial Response (PR), as assessed by the investigator per RECIST v1.1 criteria. • 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).
Secondary Endpoints
Disease Control Rate (DCR)
• Defined as the percentage of subjects in the population with a confirmed CR, confirmed PR, or Stable Disease (SD) lasting ≥6 months, as assessed by the investigator per RECIST v1.1 criteria. • 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 Response (DoR)
• Defined as the time (in months) from date of first documented evidence of confirmed CR or PR to the date of first documented progressive disease (PD), as assessed by the investigator per RECIST v1.1 criteria, or to the date of death due to any cause (whichever occurs first) among subjects with a BOR of confirmed CR or PR. • Subjects who have not shown disease progression or died at the time of analysis will be considered censored as of the date of their last evaluable disease assessment, but censoring rules for other unique scenarios (e.g., receipt of new anti-cancer therapy) will adhere those rules defined for PFS.
Progression Free Survival (PFS)
• Defined as the time (in months) from the date of first dose until the date of first documented PD, as assessed by the investigator per RECIST v1.1 criteria, or date of death due to any cause, whichever occurs first. • Subjects who have not shown disease progression or died at the time of analysis will be considered censored as of the date of their last evaluable disease assessment. Rules for determining the dates of PFS events and censoring are described in **Table 3**.

13.6.4. Safety

Adverse Events
AEs of Special Interest
• Haematopoietic thrombocytopenia Standardised MedDRA Query (SMQ) • Haemorrhages [excluding 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 Preferred Terms

ECHO/MUGA
Only the post-baseline assessments that use the same method (i.e., ECHO or MUGA) and 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.

Extent of Exposure
• Number of days of exposure to GSK525762 will be calculated based on the formula: o Duration of Exposure in Days = Treatment Stop Date – Treatment Start Date + 1. • Number of days of exposure to fulvestrant will be calculated based on the formulas: o Duration of Exposure in Days = ([Treatment Stop Date + 13] –Treatment Start Date) + 1, if the last dose date is the first two doses. o Duration of Exposure in Days = ([Treatment Stop Date + 27] –Treatment Start Date) + 1, if the last dose date is not the first two doses. • Subjects 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 calculated based on the formula: o Cumulative Dose = Sum of (Number of Days x Total Daily Dose) • The cumulative dose for fulvestrant will be calculated based on the formula: o Cumulative Dose = Sum of (Total Daily Dose) • The relative dose intensity for GSK525762 will be calculated based on the formula: o Relative Dose Intensity (%) = (Dose Intensity / Planned Dose Intensity) x 100.

Laboratory Parameters
If a laboratory value that is expected to have a numeric value for summary purposes has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. Example 1: 2 Significant Digits = '< x' becomes x – 0.01 Example 2: 1 Significant Digit = '> x' becomes x + 0.1 Example 3: 0 Significant Digits = '< x' becomes x – 1

13.6.5. Value Evidence and Outcomes

EORTC QLQ-C30 and EORTC QLQ-BR23

- Both the QLQ-C30 and the QLQ-BR23 are composed of multi-item scales and single-item measures. The QLQ-C30 includes a global health status/QoL scale, five functional scales, and nine symptom scales/items. The QLQ-BR23 includes five functional scales and four symptom scales/items.
- Each of the multi-item scales includes a different set of items; no item occurs in more than one scale.
- All 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 the global health status/QoL** represents a *high QoL*, and
  - a **high score for a functional scale** represents a *high/healthy level of functioning*, 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 to calculate 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:

(1) Calculate the raw score:

$RawScore =$ CCI [redacted]

(2) Apply the linear transformation to 0-100 to obtain the score S:

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

Range is the difference between the maximum possible value of *RS* and the minimum possible value. Both questionnaires have 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 QLQ-C30 items contributing to 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

EORTC QLQ-C30 and EORTC QLQ-BR23

	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. "very much" 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.

CCI , is not applicable if item CCI is "CCI ."
CCI , is not applicable if item CCI is "CCI ."

EORTC QLQ-BR23

	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.

EORTC QLQ-C30 and EORTC QLQ-BR23

*Items for the scales marked * are scored positively (i.e., "very much" 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.

CCI is not applicable if item CCI is "CCI."
CCI, is not applicable if item CCI is "CCI."

PRO-CTCAE

- The response frequency distribution and proportion of subjects for each PRO-CTCAE item will be presented by visit. This should be grouped first by visit, then by related term.
- Subjects who do not have a response due to skipping patterns should be reported as "Not applicable". Other subjects who do not provide a response or have withdrawn from the study should 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; 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 dropouts, 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 summarised 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, based on the following criteria:
  - 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 the FDA, report the results of PRO-CTCAE alongside the corresponding clinician-graded CTCAE results.

PRO-CTCAE
• 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 response values (0-4, null for missing) for all PRO-CTCAE Items by subject and visit.

13.7. Appendix 7: Reporting Standards for Missing Data

13.7.1. Premature Withdrawals

Element	Reporting Detail
General	• The study will be considered completed for purposes of final analysis when approximately 70% of enrolled subjects have died. However, as originally planned, the study can be stopped due to toxicity or futility before this time-point when there is enough evidence to conclude as such. • Given current study status, the totality of Phase I data assessed at the interim analysis does not support continuing investigation of GSK525762 (molibresib) in combination with fulvestrant for the treatment of HR+/HER2- advanced or metastatic breast cancer patients. As interim data failed to demonstrate meaningful clinical benefit in this patient population, enrolment into the study is now closed and the study will not incorporate Phase II. • With the implementation of Amendment 06, specific assessments and collection of survival follow-up data will no longer be required. The study will conclude when the last subject has completed/discontinued study treatment and completed the end of treatment visit. • All available data from subjects who have 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 occur when any requested data are not provided, leading to blank fields on the collection instrument: • 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 are excluded from the table. • 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.

13.7.3. Handling of Missing and Partial Dates

Imputed partial dates can be used to derive study day, duration (e.g. duration of adverse events), or elapsed time variables. 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: o 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. o 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

Element	Reporting Detail
	events will be missing. If completely missing start dates, TEAE flag is Yes. • Start or end dates of which are completely missing (i.e., no year specified) will remain missing, with no imputation applied.
Anti-Cancer Therapy (including Radiotherapy) and Surgical Procedures	• Completely missing start dates will remain missing, with no imputation applied. • Partial start dates will be imputed using the following convention: o If both month and day are missing, no imputation will be applied. o 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. • Completely or partially missing end dates will remain missing, with no imputation applied.
Concomitant Medications, Medical History, and 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, and, where applicable, Radiotherapy and 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.

Element	Reporting Detail
	• 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.
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 date of the data cutoff, o date of withdrawal from the study, or o death date. • 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, National Cancer Institute Common Terminology Criteria for Adverse Events (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

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	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)
		≥ 140	< 160 (Grade 2)
			≥ 160 (Grade 3)
Diastolic Blood Pressure	mmHg	> 80	< 90 (Grade 1)
		≥ 90	< 100 (Grade 2)
			≥ 100 (Grade 3)
Heart Rate	bpm	< 60	> 100
Temperature	Degrees C	≤ 35	≥ 38

13.8.4. Left Ventricular Ejection Fraction

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

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'.

13.9. Appendix 9: Population Pharmacokinetic (PopPK) Analyses

Not applicable.

13.10. Appendix 10: Abbreviations & Trademarks

13.10.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
AI	Aromatase Inhibitor
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical-Therapeutic-Chemical
BOR	Best Overall Response
BP	Blood Pressure
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling and Simulation
CR	Complete Response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DBF	Database Freeze
DBR	Database Release
DCR	Disease Control Rate
DL	Dose Level
DLT	Dose-Limiting Toxicity
DoR	Duration of Response
DP	Decimal Place
DS	Disposition Dataset
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30
EORTC-QLQ-BR23	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Breast-23
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
HLGT	High Level Group Term
HR+/HER2− BC	Hormone Receptor-Positive/HER2-Negative Breast Cancer
IA	Interim Analysis
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
IM	Intramuscular(ly)
INR	International Normalized Ratio
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
mTPI	Modified Toxicity Probability Interval

Abbreviation	Description
MUGA	Multiple Gated Acquisition
NCI	National Cancer Institute
NE	Not Evaluable
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetic
PR	Partial Response or ECG parameter (context dependent)
PRO	Patient Reported Outcomes
PT	Preferred Term
QTcF	Frederica's QT Interval Corrected for Heart Rate
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
RS	Response Dataset
RUCAM	Roussel Uclaf Causality Assessment Method
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SD	Standard Deviation or Stable Disease (context dependent)
SDTM	Study Data Tabulation Model
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SOP	Standard Operation Procedure
TEAE	Treatment-Emergent Adverse Event
TFL	Tables, Figures, and Listings
ULN	Upper Limit of Normal

13.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

13.11. Appendix 11: List of Data Displays

13.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.22	N.A.
Efficacy	2.1 to 2.3	2.1 to 2.3
Safety	3.1 to 3.51	N.A.
Pharmacokinetic	4.1 to 4.8	4.1 to 4.5
Section	**Listings**	
ICH Listings	1 to 50	
Other Listings	51 to 71	

13.11.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 12: 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.'

13.11.3. Deliverables

Delivery	Description
IA	Interim Analysis
RP2D	Recommended Phase 2 Dose Analysis
SAC	Final Statistical Analysis Complete for Phase I

13.11.4. 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		RP2D, SAC
1.2.	All Screened	ES6	Summary of Screening Status and Reasons for Screen Failure		SAC
1.3.	All Treated	SD4	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	Order the Reasons as displayed in the eCRF; present treatment status and reasons separately for GSK525762, fulvestrant, and overall within the same table.	IA, RP2D, SAC
Populations Analysed					
1.4.	All Screened	SP1	Summary of Study Population		IA, RP2D, SAC
Protocol Deviations					

1.5.	All Treated	DV1	Summary of Major Protocol Deviations		RP2D, SAC
Demographic and Baseline Characteristics					
1.6.	All Treated	DM1	Summary of Demographic Characteristics		IA, RP2D, SAC
1.7.	All Treated	DM6	Summary of Race and Racial Combinations		RP2D, SAC
1.8.	All Treated	DM11	Summary of Age Ranges		RP2D, SAC
1.9.	All Treated	PS1A	Summary of ECOG Performance Status at Baseline	Only include baseline visit from standard.	RP2D, SAC
1.10.	All Treated	LA1	Summary of Disease Burden at Baseline		RP2D, SAC
1.11.	All Treated	DC1	Summary of Disease Characteristics at Initial Diagnosis		IA, RP2D, SAC
1.12.	All Treated	DC2	Summary of Disease Characteristics at Screening		IA, RP2D, SAC
1.13.	All Treated	MD1	Summary of Metastatic Disease at Screening		RP2D, SAC
Prior and Concomitant Medications					
1.14.	All Treated	MH1	Summary of Past Medical Conditions		RP2D, SAC
1.15.	All Treated	MH1	Summary of Current Medical Conditions		RP2D, SAC
1.16.	All Treated	OSP1	Summary of Prior Cancer-Related Surgical Procedures		RP2D, SAC
1.17.	All Treated	OSP1	Summary of On-Treatment Cancer-Related Surgical Procedures		RP2D, SAC

1.18.	All Treated	CM8	Summary of Concomitant Medication by Ingredient	Medications to be sorted in descending order of overall incidence.	RP2D, SAC
Anti-Cancer Therapies					
1.19.	All Treated	AC1	Summary of Prior Anti-Cancer Therapy	Present all therapies (including radiotherapies).	IA, RP2D, SAC
1.20.	All Treated	CM1	Summary of Prior Dictionary Coded Anti-Cancer Therapy		RP2D, SAC
1.21.	All Treated	AC3	Summary of Number of Anti-Cancer Therapy Regimens		RP2D, SAC
1.22.	All Treated	AC4	Summary of Best Response to Prior Anti-Cancer Therapy		RP2D, SAC

13.11.5. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Overall Response Rate					

2.1.	Modified All Treated	RE1a	Summary of Investigator Assessed Best Response (RECIST v1.1 Criteria)	Show all categories of BOR, including CR and PR each split up into confirmed and unconfirmed. Categories would then include: CR confirmed, CR, unconfirmed, PR confirmed, PR unconfirmed, SD, PD, and NE. Also, include ORR and DCR (as defined in this RAP).	IA, SAC
Secondary Endpoints					
2.2.	Modified All Treated	TTE6	Summary of Duration of Response		RP2D, SAC
2.3.	Modified All Treated	TTE6	Summary of Progression-Free Survival	Produce only if data warrant.	RP2D, SAC

13.11.6. 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 Percent Reduction from Baseline in Tumour Measurement (Target Lesions)	The plot will be color-coded for best overall response with confirmation. Indication of the subject number and dose and cohort will be provided below the	IA, RP2D, SAC

				plot. Max percent reduction will be based on target lesions.	
2.2.	Modified All Treated	Non-Standard 1	Spider Plot of Percent Change from Baseline in Target Lesion Diameter		IA, RP2D, SAC
2.3.	Modified All Treated	TTE10	Kaplan-Meier Plot of Progression-Free Survival		RP2D, SAC

13.11.7. 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	In OEX1, the time on study treatment categories can be modified if necessary.	IA, RP2D, SAC
3.2.	All Treated	OEX5	Summary of Exposure to Fulvestrant	In OEX5, the categories of number of subjects who received a given number of cycles can be modified if necessary.	IA, RP2D, SAC
3.3.	All Treated	ODMOD1	Summary of Dose Delays/Interruptions of GSK525762	This may be replaced by a listing if minimal data available.	RP2D, SAC

3.4.	All Treated	ODMOD1	Summary of Dose Reductions of GSK525762	This may be replaced by a listing if minimal data available.	RP2D, SAC
3.5.	All Treated	ODMOD8	Summary of Dose Escalations of GSK525762	This may be replaced by a listing if minimal data available.	RP2D, SAC
3.6.	All Treated	ODMOD3	Summary of Dose Delays/Interruptions of Fulvestrant		RP2D, SAC
3.7.	All Treated	ODMOD1	Summary of Dose Reductions of Fulvestrant		RP2D, SAC
3.8.	All Treated	ODMOD4	Summary of Missed Doses of Fulvestrant		RP2D, SAC
3.9.	All Treated	AE19	Summary of Dose-Limiting Toxicities during the Determinative Period		RP2D, SAC
Adverse Events					
3.10.	All Treated	AE13	Adverse Event Overview		IA, SAC
3.11.	All Treated	AE16	Summary of All Adverse Events by System Organ Class and Preferred Term		RP2D, SAC
3.12.	All Treated	AE5B	Summary of Adverse Events of Special Interest Regardless of Relatedness		IA, RP2D, SAC
3.13.	All Treated	AE5B	Summary of Adverse Events of Special Interest by Maximum Grade Regardless of Relatedness		RP2D, SAC

3.14.	All Treated	AE5B	Summary of Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Grade	Include Any Treatment-Related, GSK525762-Related, and Fulvestrant-Related in the same table, with separate headers and starting on separate pages.	RP2D, SAC
3.15.	All Treated	AE5B	Summary of All Adverse Events by System Organ Class and Preferred Term and Maximum Grade		IA, RP2D, SAC
3.16.	All Treated	AE13	Summary of Grade 3-4 Adverse Events Overview		RP2D, SAC
3.17.	All Treated	AE3	Summary of Drug-Related Adverse Events by Maximum Grade 3-4	Include Total Column. Include Any Treatment-Related, GSK525762-Related, and Fulvestrant-Related in the same table, with separate headers and starting on separate pages.	RP2D, SAC
3.18.	All Treated	AE3	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment	Include Any Treatment, GSK525762, and Fulvestrant in the same table, with separate headers and starting on separate pages.	IA, RP2D, SAC
3.19.	All Treated	AE3	Summary of Adverse Events Leading to Dose Reductions in Study Treatment	Include Any Treatment, GSK525762, and Fulvestrant in the same table, with separate headers and starting on separate pages.	IA, RP2D, SAC

3.20.	All Treated	AE3	Summary of Adverse Events Leading to Dose Delays or Interruptions in Study Treatment	Include Any Treatment, GSK525762, and Fulvestrant in the same table, with separate headers and starting on separate pages.	IA, RP2D, SAC
3.21.	All Treated	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		RP2D, SAC
3.22.	All Treated	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		RP2D, SAC
3.23.	All Treated	AE3	Summary of Drug-Related Serious Adverse Events	Include Any Treatment-Related, GSK525762-Related, and Fulvestrant-Related in the same table. Page by these categories with header description in top left-hand corner.	IA, RP2D, SAC
3.24.	All Treated	AE20	Summary of Drug-Related Non-Fatal Serious Adverse Events	Include Any Treatment-Related, GSK525762-Related, and Fulvestrant-Related in the same table. Page by these categories with header description in top left-hand corner.	RP2D, SAC
3.25.	All Treated	AE3	Summary of Adverse Events Classified as Dose-Limiting Toxicities (DLTs)		RP2D, SAC

3.26.	All Treated	ESI1	Summary of Characteristics of Adverse Events of Special Interest	This table will be presented individually for each category of AESI.	SAC
3.27.	All Treated	ESI2b	Summary of Onset and Duration of the First Occurrence of Adverse Events of Special Interest	This table will be presented individually for each category of AESI.	SAC
3.28.	All Treated	DD1	Summary of Deaths		RP2D, SAC
Laboratory: Chemistry					
3.29.	All Treated	LB1	Summary of Chemistry Changes from Baseline		SAC
3.30.	All Treated	LB18	Summary of Chemistry Grade Changes from Baseline	For lab tests that are graded, include worst-case changes.	RP2D, SAC
3.31.	All Treated	LB3	Summary of Chemistry Changes from Baseline with Respect to the Normal Range	For lab tests that are graded, include worst-case changes.	RP2D, SAC
Laboratory: Haematology					
3.32.	All Treated	LB1	Summary of Haematology Changes from Baseline		SAC
3.33.	All Treated	LB18	Summary of Haematology Grade Changes from Baseline	For lab tests that are graded.	RP2D, SAC
3.34.	All Treated	LB3	Summary of Haematology Changes from Baseline with Respect to the Normal Range	For lab tests that are graded.	RP2D, SAC

Laboratory: Liver Events					
3.35.	All Treated	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting		SAC
3.36.	All Treated	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities Including Possible Hy's Law Cases	Summarize by ascending dose level and total. Possible Hy's law cases will be defined as any event of either: (a) ALT ≥3 × the upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or (b) ALT ≥3 × ULN and INR >1.5, if INR is 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.	SAC

Urinalysis					
3.37.	All Treated	UR1	Summary of Worst-Case Urinalysis Result Increases from Baseline	Include tests done by Dipstick – Specific gravity, pH, Glucose, Protein, Blood, Ketones.	RP2D, SAC
3.38.	All Treated	LB18	Summary of Urinalysis Grade Changes from Baseline	For lab tests that are graded.	RP2D, SAC
Coagulation					
3.39.	All Treated	LB3	Summary of Coagulation Changes from Baseline with Respect to Normal Range		SAC

Vital Signs					
3.40.	All Treated	VS1	Summary of Vital Signs	Include all parameters (heart rate, diastolic blood pressure, systolic blood pressure, respiratory rate, and temperature).	RP2D, SAC
3.41.	All Treated	VS1	Summary of Vital Sign Changes from Baseline	Again, show changes from baseline for all parameters (heart rate, diastolic blood pressure, systolic blood pressure, respiratory rate, and temperature).	RP2D, SAC
ECG					

3.42.	All Treated	EG1	Summary of ECG Findings		RP2D, SAC
3.43.	All Treated	EG2	Summary of Change from Baseline in ECG Values		RP2D, SAC
3.44.	All Treated	EG10A	Summary of Maximum QTcF Value Post-Baseline Relative to Baseline	Include QTcF > 500 msec. Include footnote for baseline definition. Specify the data source in the title (i.e., local read vs. central read). Also, add footnote: "Only the post-baseline assessments that used the same source as the baseline assessment (i.e., local or central cardiologist read) are used to derive change from baseline."	RP2D, SAC
3.45.	All Treated	EG11A	Summary of Maximum Increase in QTcF Values Post-Baseline Relative to Baseline	Include QTcF > 500 msec. Include footnote for baseline definition. Specify the data source in the title (i.e., local read vs. central read). Also, add footnote: "Only the post-baseline assessments that used the same source as the baseline assessment (i.e., local or central	RP2D, SAC

				cardiologist read) are used to derive change from baseline."	
Performance Status					
3.46.	All treated	PS1A	Summary of ECOG Performance Status		RP2D, SAC
3.47.	All treated	PS3A	Summary of Change in ECOG Performance Status from Baseline		RP2D, SAC
Left Ventricular Ejection Fraction					
3.48.	All Treated	OLVEF1A	Summary of Change from Baseline in Left Ventricular Ejection Fraction		RP2D, SAC
Value Evidence and Outcomes					
3.49.	All Treated	SF4_NS2	Summary of and Change from Baseline in EORTC-QLQ-C30		SAC
3.50.	All Treated	SF4_NS2	Summary of and Change from Baseline in QLQ-BR23		SAC
3.51.	All Treated	SF4_NS2	Summary of and Change from Baseline in PRO-CTCAE		SAC

13.11.8. 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 Dose Level and Cohort	Use descriptive statistics (n, mean, SD, median, min and max) by planned relative assessment time; concentrations in ng/mL	RP2D, SAC
4.2.	PK	PK01	Summary of GSK3529246 Pharmacokinetic Concentration-Time Data by Dose Level and Cohort	Use descriptive statistics (n, mean, SD, median, min and max) by planned relative assessment time; concentrations in ng/mL	RP2D, SAC
4.3.	PK	PK01	Summary of Total Active Moiety of GSK525762 Pharmacokinetic Concentration-Time Data by Dose Level and Cohort	Use descriptive statistics (n, mean, SD, median, min and max) by planned relative assessment time; TAM concentration in nM	RP2D, SAC
4.4.	PK	PK01	Summary of Fulvestrant Pharmacokinetic Concentration-Time Data by Dose Level and Cohort	Summary presented only for pre-dose as fulvestrant samples are collected only at pre-dose; use descriptive statistics (n, mean, SD, median, min and max) by planned relative assessment time; concentrations in ng/mL	RP2D, SAC

Pharmacokinetic Parameters					
4.5.	PK	PK06	Summary of Derived GSK525762 Pharmacokinetic Parameters	PK parameters: C_{max}, T_{max}, C_{trough} determined from the concentration-time data in ng/ml and in nM after conversion from ng/mL to nM; descriptive summaries: mean, SD, median, min, max, geometric mean & SD, CV%, and 95%CI of log-transformed parameters, if applicable	RP2D, SAC
4.6.	PK	PK06	Summary of Derived GSK3529246 Pharmacokinetic Parameters	PK parameters: C_{max}, T_{max}, C_{trough} determined from the concentration-time data in ng/ml and in nM after conversion from ng/mL to nM; descriptive summaries: mean, SD, median, min, max, geometric mean & SD, CV%, and 95%CI of log-transformed parameters, if applicable	RP2D, SAC
4.7.	PK	PK06	Summary of Derived Total Active Moiety of GSK525762 Pharmacokinetic Parameters	PK parameters: C_{max}, T_{max}, C_{trough} determined from the concentration-time data after conversion from ng/mL to nM; descriptive summaries: mean, SD, median, min, max, geometric mean & SD, CV%, and 95%CI of log-transformed parameters, if applicable	SAC

4.8.	PK	PK06	Summary of Derived Fulvestrant Pharmacokinetic Parameters	PK parameters: C_{max}, T_{max}, C_{trough} determined from the concentration-time data in ng/ml and in nM after conversion from ng/mL to nM; descriptive summaries: mean, SD, median, min, max, geometric mean & SD, CV%, and 95%CI of log-transformed parameters, if applicable	RP2D, SAC

13.11.9. Pharmacokinetic figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Drug Concentration Measure					
4.1.	PK	PK17	Overlay of Mean GSK525762 (nM), Mean GSK3529246 (nM), and Mean Total Active Moiety of GSK525762 (nM) Concentration-Time Curves	Include both Wk1 and Wk3 (on separate plots within the panel) and, for each, show both linear and semi-log curves.	SAC
4.2.	PK	PK18	Overlay of Median GSK525762 (nM), Median GSK3529246 (nM), and Median Total Active Moiety of GSK525762 (nM) Concentration-Time Curves	Include both Wk1 and Wk3 (on separate plots within the panel) and, for each, show both linear and semi-log curves.	SAC

4.3.	PK	PK16	GSK525762 (ng/mL) Concentration-Time Curves by Dose Level/Cohort and Week	Overlay the curves for the different dose level/cohorts on the same plot but show separate plots within the panel for Wk 1 and Wk 3; concentration in ng/mL.	SAC
4.4.	PK	PK16	GSK3529246 (ng/mL) Concentration-Time Curves by Dose Level/Cohort and Week	Overlay the curves for the different dose level/cohorts on the same plot but show separate plots within the panel for Wk 1 and Wk 3; concentration in ng/mL.	SAC
4.5.	PK	PK16	Total Active Moiety of GSK525762 (nM) Concentration-Time Curves by Dose Level/Cohort and Week	Overlay the curves for the different dose level/cohorts on the same plot but show separate plots within the panel for Wk 1 and Wk 3; concentration in nM.	SAC

13.11.10. 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		RP2D, SAC
2.	All Screened	ES7	Listing of Reasons for Screen Failure		SAC
3.	All Treated	SD2	Listing of Reasons for Study Treatment Discontinuation		RP2D, SAC
Populations Analysed					
4.	All Screened	SP3	Listing of Subjects Excluded from Any population		RP2D, SAC

Protocol Deviations					
5.	All Treated	DV2	Listing of Protocol Deviations		RP2D, SAC
6.	All Treated	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
Baseline and Disease Characteristics					
7.	All Treated	DM2	Listing of Demographic Characteristics		RP2D, SAC
8.	All Treated	DM9	Listing of Race		RP2D, SAC
Treatment Exposure					
9.	All Treated	TA1	Listing of Planned and Actual Treatments		RP2D, SAC
10.	All Treated	COMP3C	Listing of GSK525762 Drug Accountability		RP2D, SAC

11.	All Treated	OEX3a	Listing of Exposure Data to GSK525762		RP2D, SAC
12.	All Treated	OEX8B	Listing of Exposure Data to Fulvestrant		RP2D, SAC
13.	All Treated	ODMOD10A	Listing of Dose Reductions for GSK525762		RP2D, SAC
14.	All Treated	ODMOD10A	Listing of Dose Reductions for Fulvestrant		SAC
15.	All Treated	ODMOD11A	Listing of Dose Interruptions/Delays for GSK525762		RP2D, SAC
16.	All Treated	ODMOD11A	Listing of Dose Interruptions/Delays for Fulvestrant		RP2D, SAC
17.	All Treated	ODMOD11A	Listing of Missed Doses for Fulvestrant		RP2D, SAC
18.	All Treated	ODMOD15A	Listing of Dose Escalations for GSK525762		RP2D, SAC
Adverse Events					
19.	All Treated	OAE04	Listing of All Adverse Events		RP2D, SAC
20.	All Treated	OAE03	Listing of Subject Numbers for Individual Adverse Events		RP2D, SAC
21.	All Treated	OAE04	Listing of Dose-Limiting Adverse Events		RP2D, SAC
22.	All Treated	AE2	Listing of Relationship Between Adverse Event System Organ Class, Preferred Term and Verbatim Text		SAC
Serious and Other Significant Adverse Events					
23.	All Treated	OAE04	Listing of Fatal Serious Adverse Events		RP2D, SAC

24.	All Treated	OAE04	Listing of Non-Fatal Serious Adverse Events		RP2D, SAC
25.	All Treated	OAE04	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment	Based on Action taken question on AE/SAE.	RP2D, SAC
26.	All Treated	OAE04	Listing of Adverse Events Leading to Dose Reductions for any Study Drug		RP2D, SAC
27.	All Treated	OAE04	Listing of Adverse Events Leading to Dose Interruptions/Delays for any Study Drug		RP2D, SAC
28.	All Treated	AE14	Listing of Reasons for Considering as a Serious Adverse Event		SAC
29.	All Treated	OAE04	Listing of Adverse Events of Special Interest		SAC
Dose-Limiting Toxicity					
30.	All Treated	DL3	Listing of Dose-Limiting Toxicities during the Determinative Period		RP2D, SAC
Laboratory					
31.	All Treated	LB13	Listing of Chemistry Laboratory Data for Subjects with Lab Values Outside of Normal Range		SAC
32.	All Treated	LB13	Listing of Haematology Laboratory Data for Subjects with Lab Values Outside of Normal Range		SAC
33.	All Treated	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting		SAC

34.	All Treated	LIVER13	Listing of Subjects Meeting Hepatobiliary Laboratory Criteria Post-Baseline		SAC
35.	All Treated	UR2A	Listing of Urinalysis Data for Subjects with Any Value of Potential Clinical Importance		RP2D, SAC
36.	All Treated	LB13	Listing of Coagulation and Other Laboratory data		SAC
37.	All Treated	OLB7	Listing of Coagulation and Other Laboratory Data for Subjects with Lab Values Outside of Normal Range		SAC
38.	All Treated	LB14	Listing of Laboratory Data with Character Results		SAC
Pharmacokinetic					
39.	PK	PK07	Listing of GSK525762 Pharmacokinetic Concentration-Time Data by dose level and population	In ng/mL and nM.	RP2D, SAC
40.	PK	PK07	Listing of GSK3529246 Pharmacokinetic Concentration-Time Data by dose level and population	In ng/mL and nM.	SAC
41.	PK	PK07	Listing of Total Active Moiety of GSK525762 Pharmacokinetic Concentration-Time Data by dose level and population	In nM.	SAC
42.	PK	PK07	Listing of Fulvestrant Pharmacokinetic Concentration-Time Data by dose level and population	In ng/mL.	SAC
43.	PK	PK13	Listing of Derived GSK525762 (nM) Pharmacokinetic Parameters	C_{max}, T_{max}, C_{trough}, determined from	RP2D, SAC

				concentration (ng/mL) - time data.	
44.	PK	PK13	Listing of Derived GSK3529246 (nM) Pharmacokinetic Parameters	C_{max}, T_{max}, C_{trough}, determined from concentration (ng/mL) - time data.	SAC
45.	PK	PK13	Listing of Derived Total Active Moiety of GSK525762 (nM) Pharmacokinetic Parameters	C_{max}, T_{max}, C_{trough}, determined from concentration (nM) - time data.	SAC
Efficacy					
46.	All Evaluable	RE12	Listing of Subject Best Response for Interim Review by First Dose Date	Sort by date of first dose.	IA
47.	Modified All Treated	LA2	Listing of Investigator-Assessed Target Lesions (RECIST v1.1 Criteria)		RP2D, SAC
48.	Modified All Treated	LA3	Listing of Investigator-Assessed Non-Target Lesions (RECIST v1.1 Criteria)		RP2D, SAC
49.	Modified All Treated	LA4	Listing of Investigator-Assessed New Lesions (RECIST v1.1 Criteria)		RP2D, SAC
50.	Modified All Treated	RE5	Listing of Investigator-Assessed Best Overall Responses (RECIST v1.1)		RP2D, SAC

13.11.11. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Demographic and Baseline Characteristics					
51.	All Treated	SU2	Listing of Substance Use		SAC
52.	All Treated	DC3	Listing of Disease Characteristics at Initial Diagnosis		RP2D, SAC
53.	All Treated	DC4	Listing of Disease Characteristics at Screening		RP2D, SAC
54.	All Treated	MD2	Listing of Metastatic Disease at Screening		RP2D, SAC
Prior and Concomitant Medication					
55.	All Treated	MH2	Listing of Medical Conditions	Include Prior and Current, with Status column indicating same.	RP2D, SAC
56.	All Treated	CM2	Listing of Concomitant Medications		SAC
57.	All Treated	BP4	Listing of Blood Products or Blood Supportive Care Products	Include Prior (BP4) and On-Treatment (BP5).	SAC
58.	All Treated	OSP3	Listing of Surgical Procedures	Include Prior and On-Treatment.	SAC

59.	All Treated	AE2	Listing of Relationship Between ATC Level1, Ingredient and Verbatim Text		SAC
Anti-Cancer Therapy					
60.	All Treated	AC6	Listing of All Anti-Cancer Therapy	Including Prior and Subsequent.	RP2D, SAC
61.	All Treated	AC7	Listing of Anti-Cancer Radiotherapy	Including Prior and Subsequent.	RP2D, SAC
ECG					
62.	All Treated	EG5	Listing of All ECG Findings for Subjects with an Abnormal Finding		RP2D, SAC
63.	All Treated	EG3	Listing of ECG Values for Subjects with Abnormal Values		RP2D, SAC
64.	All Treated	EG3	Listing of QTcF Values of Potential Clinical Importance		SAC
Vital Signs					
65.	All Treated	VS4	Listing of Vital Signs		SAC
66.	All Treated	OVT7A	Listing of Vital Signs with Abnormal Values		RP2D, SAC
LVEF					
67.	All Treated	OLVEF2A	Listing of Left Ventricular Ejection Fraction Results		RP2D, SAC
Laboratory					

68.	All Treated	OLB13	Listing of Laboratory Data with Character Results		SAC
Value Evidence and Outcomes					
69.	Modified All Treated	SF6	Listing of EORTC-QLQ-C30 Results		SAC
70.	Modified All Treated	SF6	Listing of EORTC-QLQ-BR23 Results		SAC
71.	Modified All Treated	SF6	Listing of PRO-CTCAE Results		SAC

13.12. Appendix 12: Example Mock Shells for Data Displays

Example Non-Standard 1
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Population: Modified All Treated (Data as of: 30MAY2013)

Figure 1
Spider Plot of Percent Change from Baseline In Target Lesion Diameter