TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	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

Development Phase: I/II

Effective Date: 06-MAY-2020

Protocol Amendment Number: 6

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2015N238773_00	2016-AUG-11	Original
2015N238773_01	2016-OCT-21	Amendment No. 1

Amendment 1 applies to all global study sites.
Based upon review and comment on the protocol by the FDA, the following changes are being implemented: Clarification of the permitted prophylactic anticoagulation therapies in Exclusion Criteria #4; Correction of the spelling of goserelin throughout the protocol; Clarification of how to read the liver algorithms in Section 5.4.1; Changes to the toxicity management guidelines in Appendix 2, Table 12 for the following: Update to the dose interruption/ reduction/discontinuation guidelines for Grade 4 thrombocytopenia; Dose reduction for subjects if QTcF ≥ 60 msec change from baseline occurs OR QTcF ≥ 500; Permanent discontinuation of study medication for subjects with troponin levels approaching the threshold for MI; Clarification on length of follow-up for subjects with LVEF increase; Monitoring of blood sugar and dose reduction guidelines for subjects with moderate to severe hypoglycemia; Dose reduction and event management for subjects with Grade 3-4 diarrhea; Dose interruption and reduction for subjects with Grade 3-4 mucositis; Dose interruption/reduction/discontinuation and event management for all Grades of pneumonitis; Dose interruption and/or reduction for subjects with Grade 3-4 other non-hematologic events.
In addition to these requested changes from the FDA, other administrative changes to the protocol include: Clarification of timing for sites to report pregnancies to GSK (24 hours versus 2 weeks, based on reproductive toxicity seen in pre-clinical GSK525762 studies); Correction of spelling errors; Correction to the Medical Monitor contact information; Correction of a typo in the Phase 1 Time and Events table; Addition of clarifying language around survival follow up after the EoT visit; Addition of clarifying language around fresh biopsies; Addition of clarifying language around the timing of CBC draws in Week 1; Addition of clarifying language to inclusion criteria #6 and exclusion criterion #1-3 around prior treatment history; Clarified wording around disease assessment schedule after Week 52; Removal of Section 5.4.3.2 Valvular Toxicity Stopping Criteria, this section is part of the GSK template guidance and not mandatory for inclusion, and there are no pre-clinical/clinical valvular toxicity findings for GSK525762. Removal of this information will also reduce the number of assessments required for subjects; Update to the option of scan (now ECHO or MUGA) performed to monitor cardiac safety; Removal of Section 7.3.5.6 Disease Related Events, this section is only to be included if there are pre-defined disease related events, and this protocol has no pre-defined events; Update to the Grade 3 and Grade 4 thrombocytopenia management guidelines to make them more stringent, based upon emerging data that will be provided in an INDSR (October 2016); Removal of the fever management guidelines in Appendix 2, Table 12, as part of the ongoing safety review for GSK525762, there is no apparent clinical correlation to the preclinical in vitro findings suggesting a potential for fever.

2015N238773_02	2017-JAN-31	Amendment No. 2
Amendment 02 applies to all sites in the United Kingdom. Based upon review and comment on the protocol by the MHRA, the following changes are being implemented as a standalone amendment for the UK: Clarification of the length of time, post treatment completion, that the approved list of contraceptives must be used by female subjects of childbearing potential; clarification in Section 5.4 that pregnancy is a reason for subject discontinuation from the study. A forthcoming amendment (03) will include these revisions as part of a global protocol amendment.		
2015N238773_03	2017-MAR-07	Amendment No. 3
Amendment 03 applies to all global study sites. Changes to the protocol include: Clarification to the prior treatment subjects may have received; update to the timelines of the study, based upon new enrollment projections; clarification of inclusion criteria #6 regarding prior treatment subjects may have received; clarification of exclusion criteria #1 and #3 regarding number of prior lines of therapy; addition of two new exclusion criteria regarding use of NSAIDS and history of bleeding events; clarification in Section 5.4 that pregnancy for subjects of childbearing potential is a cause for study discontinuation; clarification regarding the liquid that subjects are permitted to use when taking GSK525762; clarification around the dosing window for fulvestrant; addition of Table 3 which clarifies dose reductions; clarification around use of Aspirin; update to the prohibited meds table in Section 6.11.2.1 and the cautionary meds table in Section 6.11.2.3; clarification around use of medication containing acetaminophen; update to the schedule of assessments in the Time and Events tables for both Phase I and II of the study; update to the schedule of laboratory assessments in both Phase I and II of the study; update to the ± visit windows for Weeks 2, 3, 4, 5, and 9; added logistical and medical guidance around when on treatment fresh biopsies and planned surgical procedure can take place; updated the thrombocytopenia management guidelines in Table 13 to be in line with regulatory feedback; clarification of baseline imaging windows; clarification of approved contraception and length of time said contraception needs to be used post study treatment.		
2015N238773_04	2017-OCT-18	Amendment No. 4
Amendment 04 applies to all global study sites. Based upon review and comment on the protocol by the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), the following changes are being implemented: language added to Section 6.11.2.3 around concomitant medications that are substrates of CYP3A4; update to the toxicity management guidelines for QTcF monitoring in Appendix 2, Table 13; Times and Events tables in Section 7.1, updated to clarify the schedule of assessments post week 49. Additional changes to the protocol include: update to protocol authors; update to the primary GSK medical monitor, update to Sponsor signatory; ERS1 mutational status in the objectives and endpoints has been updated to exploratory, and Section 7.7 has been updated to reflect the translational analysis changes; removal of the time to progression (TTP) endpoints; update to description of Ph I enrolment during the dose escalation phase and the definition of study completion in Ph II; update to statistical analysis descriptions throughout the protocol; addition of information around the dose escalation meetings;		

Section 6.6 on the handling of GSK525762; clarification in Section 5.1, Table 2, regarding acceptability of both Troponin I or T; Times and Events tables in Section 7.1, updated to clarify ECHO/MUGA scan requirements for screening and W1D1, timing of on treatment biopsy collection in Ph I, lab assessment requirements, and length of screening window (also updated throughout the document); update to the toxicity management guidelines for QTcF re-challenge in Appendix 2, Table 13; removal of pre-defined events of interest.		
2015N238773_05	2018-SEP-11	Amendment No. 5
Amendment 05 applies to all global study sites. These changes are based upon revisions noted by the study team, and include: • Updating the protocol title to hormone receptor positive (HR+/HER2- BC) to align with the inclusion criteria which requires both ER+ and PR+ BC subjects. • Corrections made throughout to align HR+/HER2- BC with the inclusion criteria and title. • Update to clarify that dose level (DL) 2 (80 mg) has been discontinued. • Update to the author list and sponsor signatory. In introduction and Section 5.4 include requirement that the Medical Monitor (MM) should be consulted before a subject can discontinue one agent and continue on the other. Study Design in Synopsis and Section 4: Original language describing Phase I and Phase II remains. New sections added to address the updates to Phase I which include DL2 (80 mg) discontinuation, update the DL1 (60 mg) cohort 2 population to include subjects must have received greater than or equal to 12 months of prior Cyclin-Dependent Kinase (CDK)4/6+ Aromatase Inhibitor (AI) for metastatic disease and progressed while on treatment and allow bone only disease. Revision in sub-sections of Section 4.7 to be in line with wording in the most recent Investigator's Brochure. Inclusion/exclusion criteria: • Provision of a fresh tumor biopsy sample at screening; • letrozole has been expanded to include all AI agents; • prior treatment allowed in the CDK4/6 patient population; • subjects must have received greater than or equal to 12 months of prior CDK4/6+ AI for metastatic disease and progressed while on treatment; • bone only disease is allowed (screening biopsy not required after discussion with MM); • update to criteria for severe or uncontrolled systemic diseases; update to criteria for baseline QTcF). Section 5.4.2 update to QTc stopping criteria; removal of former Section 6.3.1 Guidelines for Events of Special Interest; in Section 6.11.1 include granulocyte colony-stimulating factors as a permitted medications; update to wording in Section 6.11.2.1 Prohibited Medication and removal of former Table 4; update to wording in Section 6.11.2.3 Cautionary Medication and removal of former Table 5; Clarification in Section 6.11.2.2 regarding both prescription and non-prescription herbal preparations/medications; Time and Events Table 5 and Table 8: Updates regarding electrocardiograms (ECGs),		

requirement of fresh biopsies at screening and collection window, clarification of requirements around fresh tumor biopsies sample and other general clarifications; Pregnancy Test- X has been removed from the Column for Q12wks (Wk49 and after). This was an error and Q4wks is correct. In Section 7.2.2 clarification regarding PK sample collection for subjects with interrupted dosing; Section 7.3.3.1 update to guidelines for electrocardiograms assessments; update to Table 9 Clinical Labs regarding collection of troponin and adding a list of acronyms in the footnotes; update to guidance regarding screening and on treatment biopsies in Section 7.5.1 and Section 7.7.2; update to toxicity management for QTcF events in Appendix 2 and explanation for reconsent; Collection of pregnancy information regarding elective termination is clarified that only those performed due to medical reasons are required to be reported.		
2015N238773_06	2020-MAY-06	Amendment No. 6
Amendment 06 applies to all global study sites. These changes are based on the decision to close out the study and stop all new enrolment based on interim data failing to demonstrate meaningful clinical benefit in the proposed patient population. 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 hormone receptor-positive/HER2-negative (HR+/HER2-) advanced or metastatic breast cancer patients. Enrolment into the study is now closed. The study will conclude when the last subject has completed/discontinued study treatment and completed the end of treatment visit. Changes to the protocol include: • Enrolment into the study is now closed • Removes the requirement for specific protocol assessments and survival follow-up (Section 7.1 – Time and Events Tables) • Updates to contraceptive measures required for study participants, based upon January 2020 updates to the fulvestrant Summary of Product Characteristics • Update to the GSK signatory and GSK medical monitor • Provides updated guidance for subjects who have discontinued combination treatment and are on fulvestrant monotherapy • Provides clarification on clinical supply dosages available for the study • Administrative changes including minor clarifications, formatting and typographical errors		

SPONSOR SIGNATORY

PPD

PPD

06 May 2020

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

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

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

Sponsor Legal Registered Address:

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

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

Regulatory Agency Identifying Number(s): Investigational New Drug (IND) # IND131933, EudraCT number 2016-003074-40

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 201973

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

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

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

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

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1. PROTOCOL SYNOPSIS FOR STUDY 201973

Rationale

In the United States, breast cancer is the most common malignancy in women, affecting an estimated one out of every eight females during her lifetime. Breast cancer is subdivided into multiple clinical subtypes, based on the expression of steroid hormone receptors (estrogen receptor [ER] and progesterone receptor [PR]) and the receptor tyrosine kinase erb-b2 receptor tyrosine kinase 2 (ERBB2, known clinically as HER2). ER is a transcription factor that translocates to the nucleus upon binding to estradiol and other, related sex hormones. Once inside the nucleus, it binds to deoxyribonucleic acid (DNA) at sites of open chromatin in order to drive the expression of ER-dependent genes. For the 70% of women whose tumors express ER (i.e., ER-positive breast cancer (ER+BC), endocrine therapy remains the cornerstone of therapy for most of these women, followed by cytotoxic chemotherapy once tumors no longer respond to hormonal agents. Currently, approved endocrine therapies include the ER antagonist tamoxifen; the aromatase inhibitors (AIs) anastrozole, exemestane, and letrozole; and fulvestrant, a selective ER antogonist. Recently, improved progression-free survival (PFS) has been demonstrated by combining endocrine therapy with either the Mammalian Target of Rapamycin (mTOR) inhibitor everolimus or with the cyclin-dependent kinase (CDK) 4/6 inhibitors (e.g. palbociclib). Despite these advances, however, the disease remains incurable, and relapse (and thus need for novel therapeutic agents) is inevitable.

Treatment-resistant ER+BC tumors continue to express ER, which in turn continues to bind to DNA and express ER-dependent genes. Recently, the importance of epigenetic markers in the regulation of ER-dependent gene expression has been identified. One set of proteins that is important for regulating epigenetic markers is the Bromodomain and Extraterminal (BET) family. These proteins recognize acetyl groups on the tails of histones and are critical for recruiting transcriptional machinery necessary for gene expression. BET proteins regulate a host of other downstream effectors that are critical for proliferation, differentiation, and cell survival. BET inhibitors, including GSK525762, are currently being evaluated in the therapy of both solid tumors and hematologic malignancies.

This study (201973) proposes to evaluate the combination of GSK525762, a potent inhibitor of the BET family of proteins, with fulvestrant, in women with HR+/HER2- BC. Both agents are inhibitors of distinct but convergent molecular mechanisms that are critical for growth and proliferation of breast cancer tumor cells. This is a combination Phase I and Phase II study; the objectives are to first identify a dose of GSK525762 that may be combined safely with fulvestrant, followed by a Phase II study to identify clinical activity of the drugs when given in combination.

Objective(s)/Endpoint(s)

Phase I

With the implementation of amendment 06, Phase I of the study is closed to enrolment.

Objectives	Endpoints
Primary	
• To determine a recommended Phase 2 dose (RP2D) of GSK525762, when given in combination with fulvestrant, in women with advanced or metastatic hormone receptor positive 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] data
Secondary	
• 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 the 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 CR plus PR plus stable disease [SD] rate), duration of response, and progression-free survival (PFS)
• To characterize the exposure to GSK525762 and fulvestrant, when given in combination.	• Concentrations of GSK525762, GSK525762 relevant metabolites and fulvestrant following administration in combination
Exploratory	
• 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	• Transcriptomic and/or protein changes in molecular markers of BET inhibition and ER signaling in tumor tissue
• To identify potential indicators of sensitivity or response to GSK525762 and fulvestrant, when given in combination in women with advanced or metastatic ER+BC.	• Mutational analysis of tumor tissue; correlation of baseline somatic and tumor-specific genetic and genomic profiles with response.
• 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 (TTG) predicted with the model parameters and relationship with clinical activity parameters.
• To evaluate the exposure response relationship between GSK525762 and/or fulvestrant	• Relationship between GSK525762 and/or fulvestrant exposure markers (e.g. dose, Cmin,

Objectives	Endpoints
exposure and safety and efficacy parameters.	Cmax), and safety/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

Phase II

With the implementation of amendment 06, Phase II of the study is terminated.

Objectives	Endpoints
Primary	
• To evaluate the effect of treatment with GSK525762 and fulvestrant, when given in combination, on progression-free survival in women with advanced or metastatic HR+/HER2- BC	• Progression free survival (PFS), defined as the median time from the first dose of study treatment until objective tumor progression or death from any cause, whichever comes first
Secondary	
• To evaluate the effect of treatment with GSK525762 and fulvestrant, when given in combination in women with advanced or metastatic HR+/HER2- BC, on additional metrics of subject survival	• Overall survival (OS)
• To evaluate the clinical activity of GSK525762 and fulvestrant, when given in combination	• ORR, DCR
• To characterize the exposure to GSK525762, when given in combination with fulvestrant.	• GSK525762 and metabolites concentrations following administration in combination with fulvestrant
• To characterize the exposure to fulvestrant when given alone or with GSK525762	• Fulvestrant concentrations following administration alone or in combination with GSK525762
Exploratory	
• 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
• To describe the kinetics of tumor growth in the presence or absence of GSK525762 for each	• Tumor size over time, tumor growth rate constants, and time to tumor growth (TTG)

Objectives	Endpoints
treatment and investigate the relationship between tumor growth kinetics and clinical activity	predicted with the model parameters and relationship with clinical activity parameters
• To evaluate the exposure response relationship between GSK525762 and/or fulvestrant exposure and safety and efficacy parameters • To evaluate the effect of GSK525762 and fulvestrant, when given in combination, on symptoms and quality of life • 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	• Relationship between GSK525762 and/or fulvestrant exposure markers (e.g. dose, Cmin, Cmax), and safety/efficacy parameters. • Change from baseline in EORTC-QLQ-C30 and EORTC-QLQ-BR23 questionnaires • Targeted sequencing to determine correlation between ESR1 mutations and clinical response

Overall Design

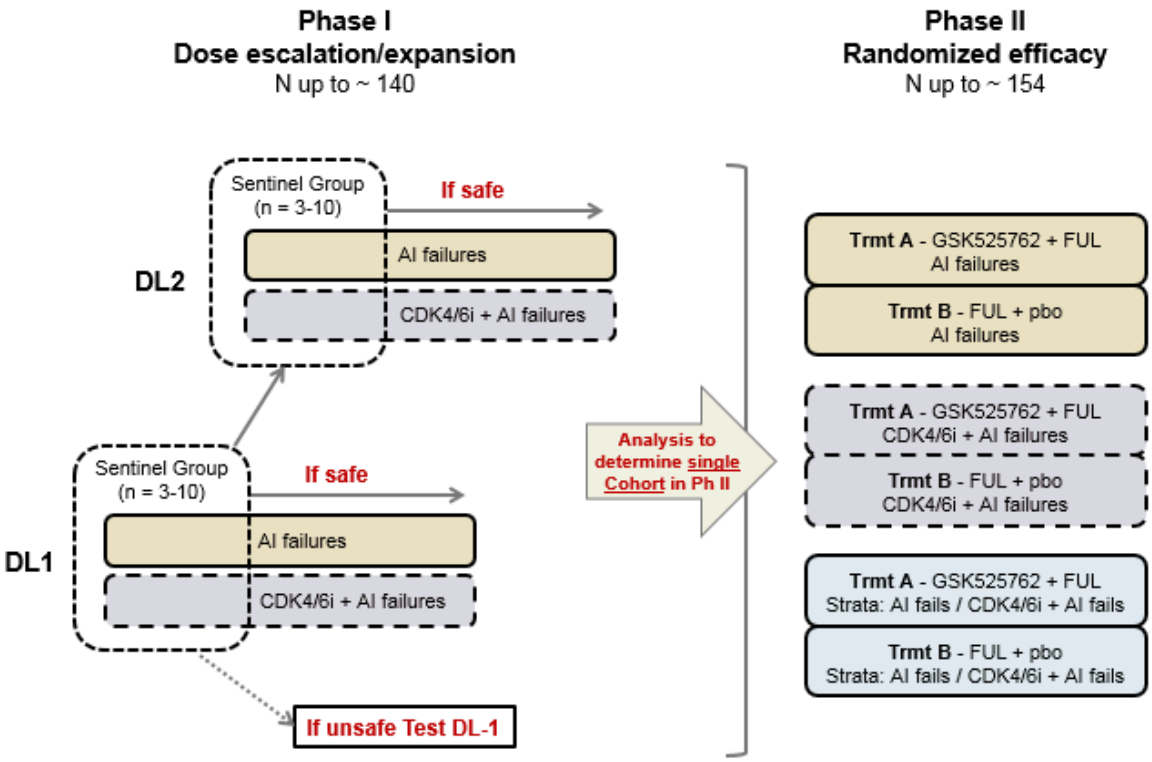
This study is a Phase I/II dose-escalation, expansion (Phase I) and randomized control (Phase II) study with oral administration of GSK525762 in combination with fulvestrant in advanced or metastatic HR+/HER2- BC subjects, who have disease that has progressed after prior treatment with at least one line of endocrine therapy.

Original Overall Design (Protocols 01-04)

Phase I of the study is designed as parallel single arm treatment with GSK525762 in combination with fulvestrant in two distinct populations of HR+/HER2- breast cancer to determine a recommended Phase 2 dose (RP2D) based on safety, tolerability, pharmacokinetic, and efficacy profiles. [Changes have been made to this Phase]

Phase II of the study is designed as a randomized, double-blind, placebo-controlled cohort, the composition of which will be selected at the end of Phase I, based upon the totality of Phase I data. This cohort will compare the efficacy of GSK525762 in combination with fulvestrant versus fulvestrant with GSK525762-matched placebo in subjects with disease that progressed on anti-estrogen and/or one or more AIs, or failure of a combination treatment with CDK4/6 inhibitor plus AI or a combination of both of these groups/patient populations.

Study Schematic



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

Phase I:

With the implementation of amendment 06, Phase I of the study is closed to enrolment.

Phase I will study the safety, tolerability, PK, and efficacy of GSK525762 plus fulvestrant when administered in combination in up to two escalating dose levels (DLs). Eligible subjects must have advanced or metastatic HR+/HER2- BC that has been refractory to, or progressed despite, prior systemic therapy. The combination of GSK525762 plus fulvestrant will be evaluated in an open-label fashion in two separate cohorts. These cohorts will be evaluated at both DLs:

- Subjects who have disease that has relapsed during treatment or within 12 months of completion of adjuvant therapy with an AI, OR disease that progressed during treatment with an AI for advanced/metastatic disease. Prior ovarian suppression and/or tamoxifen are allowed as long as the other criteria are met.
- Subjects who have disease that has progressed during treatment with the combination of a CDK4/6 inhibitor (e.g., palbociclib) plus letrozole for advanced or metastatic disease. Prior ovarian suppression and/or tamoxifen are allowed as long as the other criteria are met.

Documented progression on the last line of systemic anti-cancer therapy is required.

Phase I will follow a modified toxicity probability interval (mTPI) design. The design assumes (i) approximately 30 subjects will complete the dose-limiting toxicity (DLT) evaluation period and (ii) the true underlying toxicity rate for GSK525762 in combination with fulvestrant falls within the range from 25% to 35% and centered at 30%.

Subjects in DL1 will begin dosing with fulvestrant at the approved dose, plus GSK525762 at one dose level lower than the single-agent RP2D. Subjects will be enrolled into one of two possible cohorts, based on their prior treatment history, as defined above. A sentinel group (comprising subjects enrolled in both cohorts) of at least 3 and up to 10 subjects will be evaluated for safety. If the DLT rate of the DL1 sentinel group does not exceed the maximum permitted toxicity rate, the following will occur in parallel:

- At DL1, up to 35 subjects will be enrolled into each cohort
- Evaluation of DL2 will begin

Subjects in DL2 will begin dosing with fulvestrant at the approved dose, plus GSK525762 at the single agent RP2D. Subjects will be enrolled into one of two possible cohorts, based on their prior treatment history, as defined above. A sentinel group (comprising subjects enrolled in both cohorts) of at least 3 and up to 10 subjects will be evaluated for safety. During enrolment of the DL2 sentinel group, the enrolment for DL1 will be temporarily closed. After completing the enrolment for the sentinel group of DL2, the enrolment for DL1 will be re-opened and the enrolment for DL2 will be temporarily closed while waiting for the 28 days DLT observation period to be completed for all subjects.

If the DLT rate of the DL2 sentinel group does not exceed the maximum permitted toxicity rate, enrolment for DL2 will be re-opened and the enrolment for DL1 will be temporarily closed **until DL2 enrols the same number of subjects as DL1**. After that, both DL1 and DL2 will be open to enrolment, and subjects will be assigned 1:1 to either DL1 or DL2 until one or the other dose level is filled or terminated. All subjects would then be enrolled at the remaining dose level.

Each prior treatment history cohort (two per DL) may enroll up to 35 subjects (including subjects from the sentinel cohorts), for a total of approximately 70 subjects enrolled at each DL. The number of subjects enrolled into each cohort may vary, as interim analyses for safety and efficacy may terminate any cohort if the DLT rate exceeds the maximum permitted toxicity rate, or if the efficacy rate does not exceed the historical overall response rate (ORR).

If the DLT rate of the sentinel group in DL1 exceeds the maximum permitted toxicity rate, then a lower dose level (DL-1) will be evaluated. If the DLT rate of the sentinel group in DL2 exceeds the maximum permitted toxicity rate, then additional subjects will not be enrolled at DL2, and all subjects will be enrolled at DL1.

Subjects must have measurable disease per RECIST 1.1 criteria. The primary endpoints of Phase I of the study are safety, tolerability, and clinical response, based on ORR. Additional efficacy data, including PFS and OS, will be collected from all subjects treated in Phase I. The totality of data, including safety/tolerability, PK, and efficacy,

will be used to determine whether to proceed to Phase II, and which cohort and dose to be carried forward into Phase II.

Phase II:

With the implementation of amendment 06, Phase II of the study is terminated.

Phase II is a randomized, double-blind, placebo-controlled study that will explore the clinical activity of GSK525762 and fulvestrant when given in combination, to subjects with advanced or metastatic HR+/HER2- BC. The primary endpoint of Phase II is PFS. The design for Phase II will be finalized based on the results from Phase I.

Phase II will be composed of one cohort, the composition and the dose of which will be decided based on the totality of the data at the end of Phase I. If any of the prior treatment history-specific cohorts in Phase I are terminated early for toxicity or lack of efficacy at any dose, enrolment of subjects with those prior therapies at that dose will not be carried forward into Phase II.

Phase II may enrol subjects who have disease that has progressed after prior therapy with:

- AIs alone (either in the setting of primary metastatic disease or on-treatment/within 12 months of discontinuing adjuvant endocrine therapy), OR
- CDK4/6 inhibitor plus AI, OR
- either AI therapy OR CDK4/6 inhibitor plus AI. If both cohorts are permitted to enroll in Phase II, randomization will be stratified by prior CDK4/6 inhibitor-based therapy (i.e., CDK4/6 inhibitor-naïve versus CDK4/6 inhibitor-exposed) and corresponding stratified analysis will be provided at interim and final analyses.

Eligible subjects will be randomized 1:1 to receive GSK525762 plus fulvestrant (Arm A), or fulvestrant plus GSK525762-matched placebo (Arm B), in a double-blinded fashion. Note that subjects may have received up to one line of cytotoxic chemotherapy in the advanced/metastatic setting. In addition, subjects enrolled in the CDK4/6 inhibitor plus AI cohort may have failed therapy with any number of lines of anti-estrogens and/or AIs. Subjects will be treated until progression, toxicity, or withdrawal of consent. The primary endpoint of this Phase of the study will be progression free survival (PFS); comparison of primary and secondary endpoints will be performed between the investigational and control arms.

Revised Overall Design (Protocol Amendment 05)

While the overall study goals and design remain the same, changes have been made to Phase I of the study to address to emerging data and intended to better define the patient population most likely to benefit from combination treatment of molibresib plus fulvestrant. The following are to be noted:

1. DL1 Cohort 1 (60 mg, AI-failures) will complete enrolment to 35 subjects as under amendment 4

2. DL1 Cohort 2 (60 mg, CDK4/6 inhibitor plus AI failure) – change in inclusion criteria and to the number of subjects to be enrolled is detailed below.

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.

4. Phase II design remains unchanged – as originally stated, this Phase of the study will be redesigned based after analysis of Phase I data.

Change to DL1 Cohort 2:

- Enrolment into DL1 (60 mg) Cohort 2 is modified. Subjects previously treated with the combination of a CDK4/6 inhibitor (e.g., palbociclib) plus letrozole AI for advanced or metastatic disease will be enrolled as follows;

    - 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.

    - 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.

    - The total number of subjects enrolled into this cohort will be approximately 75.

    - Prior ovarian suppression and/or tamoxifen are allowed as long as the other criteria are met.

This requirement is based on emerging data and intended to better define the patient population most likely to benefit from combination treatment.

Treatment Arms and Duration

In Phase I, all subjects will receive GSK525762 in combination with fulvestrant. Subjects will begin combination therapy immediately, and will continue until unacceptable toxicity, progression of disease, withdrawal of consent, or death. The total duration of Phase I will depend on recruitment rates, withdrawals due to toxicity or progression or death, with an approximate duration of 15 months.

Initial administration will consist of daily GSK525762 and the approved dose/regimen of fulvestrant. Additional doses and schedules may be explored based on emerging safety, tolerability, and PK data. No doses will be explored beyond 100 mg GSK525762 or 500 mg (IM) fulvestrant, as these doses are considered to be the Maximum Feasible Dose (MFD), unless emerging PK data demonstrate reduced exposure of either drug in combination compared to single agent.

Dose interruptions and/or reductions of GSK525762 and/or fulvestrant are permitted, as necessary, in response to toxicity or other events. There will not be any pre-planned dose reductions. The decision to interrupt/reduce dosing will take into account likely attribution of toxicity, and reduction/interruption of one agent or the other will be

permitted. Subjects who require dose reduction and/or discontinuation of one investigational agent may continue on the other agent until progression, withdrawal of consent, or unacceptable toxicity after discussion with the Medical Monitor.

Initial dosing in Phase I will maintain a fixed dose of fulvestrant (500 mg intramuscularly (IM) on days 1, 15, and 29 of cycle 1 and then monthly thereafter). GSK525762 will initiate dosing at 60 mg once daily, which is one dose level lower than the single-agent RP2D. Doses beyond the single-agent RP2D may be explored if the drug is tolerated and PK analysis demonstrates reduced GSK525762 exposure (AUC and/or Cmax) when administered in combination with fulvestrant. In Phase I, a completed subject is one who is followed to death.

Phase II is a randomized, double-blind, placebo-controlled study in subjects with advanced or metastatic HR+/HER2- BC. Subjects who have disease that has progressed on prior treatment with either AIs, or a combination of a CDK4/6 inhibitor and AI will be randomized to receive the approved dose of fulvestrant (500 mg intramuscularly (IM) on Days 1, 15, and 29 of cycle 1, and monthly thereafter) in combination with GSK525762, or fulvestrant with GSK525762 matched placebo. The treatment cohort and dose taken into Phase II will be based upon the totality of data from Phase I.

In Phase II, subjects will begin therapy immediately and will continue until unacceptable toxicity, progression of disease, or withdrawal of consent. Dose adjustments of GSK525762 or fulvestrant are permitted as necessary based on toxicity or other events as noted above. The total duration of Phase II will depend on recruitment rates, withdrawals due to toxicity or progression, and the timing of subjects' duration on study, with an approximate duration of 16 months.

In Phase II, a completed subject is one who is followed until death. Any subject who progresses while receiving study treatment or discontinues treatment due to a treatment-emergent (i.e. unrelated or related to treatment) adverse event will be followed until death. The investigator is responsible for ensuring that consideration has been given for the post-study care of the subject's medical condition.

Type and Number of Subjects

Approximately 294 subjects worldwide with relapsed/refractory advanced or metastatic HR+/HER2- BC will be enrolled in the study as a whole. Subjects may have disease which progressed during or within 12 months of stopping adjuvant therapy, or disease which was initially diagnosed as advanced or metastatic. Cohort 2 is modified to include a minimum of 48 subjects who have progressed after greater than or equal to 12 months of a CDK4/6 inhibitor (e.g., palbociclib) plus AI for advanced or metastatic disease with either measurable disease (32 subjects) or bone only disease (16 subjects). In Phase I, up to 140 subjects will be treated. The total number of subjects required will depend upon the safety profile of the combinations and the number of responses, as described in the full protocol. In Phase II, approximately 154 subjects will be treated.

Analysis

For evaluation of safety, Phase I will follow a mTPI design to identify the MTD of GSK525762 when administered in combination with fulvestrant. Subject safety will be monitored continuously using a mTPI method, and individual cohort(s) may be terminated early if the toxicity exceeds pre-specified parameters. No formal statistical hypotheses will be tested. Analysis will be descriptive and exploratory. All data will be pooled, and descriptive analyses will be summarized and listed by dosing cohort at study conclusion. Dose escalation decision(s) will be based on the totality of clinical safety assessment based on a combination of reported safety events, as well as pharmacokinetic data.

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 objective response rate (CR + PR) of 25% relative to a 10% response rate suggesting no activity. This will be conducted by testing the null hypothesis that P0<=0.1 versus the alternative that P1 >0.25, 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 the measurable disease subjects only, defined as an objective response rate (CR + PR) of 20% relative to a 5% response rate suggesting no activity. This will be conducted by testing the null hypothesis that P0<=0.05 versus the alternative that 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%. This portion of the study will employ Bayesian methods that allow the study to be frequently monitored with the constraint of both Type I and Type II error rates. The first interim analysis in each cohort will be performed when at least 10 evaluable subjects have enrolled in that cohort. Enrolment to an individual cohort may be stopped early for toxicity or lack of efficacy, but cohorts will not be stopped early if the ORR meets or exceeds the alternate hypothesis at the interim analyses.

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. Enrolment into the study is now closed as interim data failed to demonstrate meaningful clinical benefit in this patient population.

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. There will be no Phase II.

In Phase II, the primary goal is to demonstrate a clinically meaningful improvement in PFS when GSK525762 is added to fulvestrant therapy. For this study, “clinically meaningful” is defined as a hazard ratio (HR) of 0.5, indicating that the combination therapy doubles the PFS relative to the comparator arm. The study will have 90% power to detect a hazard ratio (HR) of 0.5 with a one-sided 0.025 level test. A planned interim

analysis will be performed when 45 subjects have progressed or died; the study may be stopped at the time of interim analysis for safety as well as for futility or efficacy.

2. INTRODUCTION

GSK525762 is a novel inhibitor of Bromodomain and Extraterminal (BET) proteins currently under investigation to treat a number of human malignancies. Fulvestrant induces selective degradation of the estrogen receptor (ER). Together, they demonstrate synergistic effects against tumor cell growth in treatment-resistant breast cancer cell lines *in vitro* and *in vivo*. The current protocol (study 201973) aims to test the safety, tolerability, PK, PD, and efficacy of this combination when administered concomitantly to women with advanced or metastatic Hormone Receptor-positive/HER2-negative (HR+/HER2-) breast cancer (HR+/HER2- BC).

2.1. Study Rationale

Advanced or metastatic HR+/HER2- BC is an incurable illness that will prove fatal for the majority of afflicted women. Current standards of care (SoC) include endocrine therapy, targeted therapy, and chemotherapy. Recent preclinical data suggest that altering the expression of the HR as well as other HR-responsive genes may provide therapeutic benefit for women for whom endocrine therapy alone has proven inadequate. One potential novel target for therapy is the BET family of proteins. These proteins bind to chromatin and regulate gene expression, and data suggest that combination with endocrine therapy may provide therapeutic benefit and even restore sensitivity to HR-targeted agents. The current protocol (201973) proposes to evaluate the combination of the BET inhibitor GSK525762 with the ER-degrading agent fulvestrant in women with metastatic or advanced HR+/HER2- BC who have progressed on at least one line of prior endocrine therapy.

2.2. Brief Background

In the United States, breast cancer is the most common malignancy in women, affecting an estimated one out of every eight females during her lifetime [Siegel, 2016]. While many cases of hormone receptor positive breast cancer can be treated definitively with a multi-modal approach of surgery, radiation, and/or hormonal manipulation, metastatic breast cancer remains an incurable disease for which current approaches are palliative. Given the prevalence of this disease, breast cancer remains an active area of clinical development.

Breast cancer is subdivided into multiple clinical subtypes, based on the expression of steroid hormone receptors (estrogen receptor [ER] and progesterone receptor [PR]) and the receptor tyrosine kinase erb-b2 receptor tyrosine kinase 2 (ERBB2, known clinically as HER2). The expression of these factors contributes to assessing the overall prognosis of the disease and drives therapeutic decision-making. ER is a transcription factor that translocates to the nucleus upon binding to estradiol and other, related sex hormones. Once inside the nucleus, it binds to deoxyribonucleic acid (DNA) at sites of open chromatin in order to drive the expression of ER-dependent genes [Ross-Innes, 2012; Feng, 2014]. For the 70% of women [McNeil, 2006] whose tumors express the ER (i.e., ER-positive breast cancer (ER+BC), endocrine therapy remains the cornerstone of therapy for most of these women, followed by cytotoxic chemotherapy once tumors no longer respond to hormonal agents. Currently, approved endocrine therapies include the

ER antagonist tamoxifen; the aromatase inhibitors (AIs) anastrozole, exemestane, and letrozole; and fulvestrant, a selective ER antagonist. Recently, improved progression-free survival (PFS) has been demonstrated by combining endocrine therapy with either the Mammalian Target of Rapamycin (mTOR) inhibitor everolimus [Baselga, 2012] or with the cyclin-dependent kinase (CDK) 4/6 inhibitor palbociclib [Finn, 2015]. Despite these advances, however, the disease remains incurable, and relapse (and thus need for novel therapeutic agents) is inevitable. While patients proceed from one therapy to the next, they ultimately exhaust their options, ER HR+/HER2- BC an area of unmet need, as a result of this inexorable progression.

The mechanisms by which ER+BC tumors become resistant to endocrine therapy have been extensively investigated in recent years. These include upregulation of growth factor receptor signalling pathways, mutations in the ER, and modulation of pathways that render BC cells more sensitive to estrogen [McNeil, 2006]. Upregulation of v-myc avian myelocytomatosis viral oncogene homolog (c-myc) and B-cell CLL/lymphoma 2 (BCL2) gene products have been demonstrated to be critical for growth of ER+BC cells and tumors both in vitro and in vivo [Chrzan, 2001; Miller, 2011; Planas-Silva, 2007; McNeil, 2006]. These alterations lead to broad changes in gene expression that drive proliferative and anti-apoptotic effects within the tumor cells, and ultimately to tumor growth despite treatment with anti-estrogen therapy [Miller, 2011].

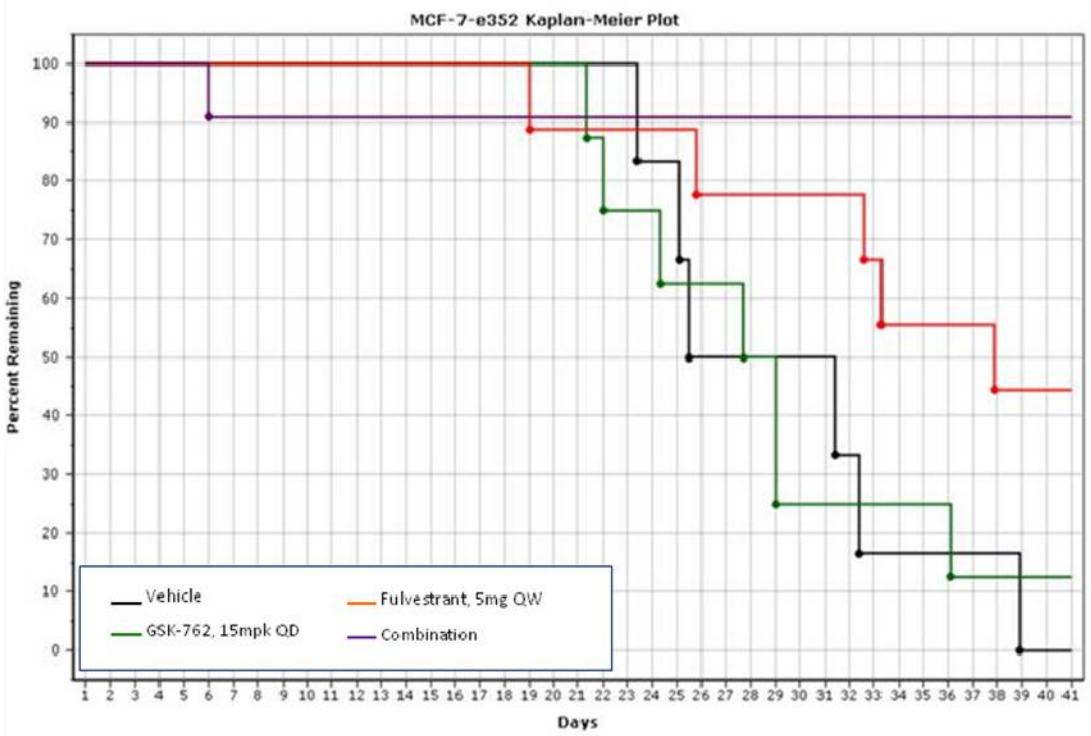
Treatment-resistant ER+BC tumors continue to express ER, which in turn continues to bind to chromatin and express ER-dependent genes [Ross-Innes, 2012]. This suggests that agents that directly downregulate ER expression and/or modulate ER binding to chromatin may lead to biologic and/or clinical responses. Recently, the importance of epigenetic markers in the regulation of gene expression has been identified. Cells possess machinery for post-translational modification (such as acetylation, methylation, or phosphorylation) of specific residues on histone tails. These modifications “mark” those regions of chromatin for enhancement or silencing of gene expression. The mechanism and importance of this “histone code” is only now being unravelled, and cells express enzymes for “writing” (i.e., transferring molecular moieties onto histone tails), “erasing” (i.e., removing those moieties when they are no longer required), and “reading” (i.e., identifying those marks and recruiting necessary machinery to have an effect on gene expression).

One subset of these “readers” is the Bromodomain and Extraterminal (BET) family. These proteins recognize acetyl groups on the tails of histones and are critical for recruiting transcriptional machinery necessary for gene expression. BET proteins regulate a host of other downstream effectors that are critical for proliferation, differentiation, and cell survival. BET inhibitors are currently being evaluated in the therapy of both solid tumors and hematologic malignancies. GSK525762, is currently being studied in two separate trials: BET115521 and BET116183. Both are Phase I/II studies, with the primary endpoint to evaluate safety and tolerability of GSK525762 and identify the single-agent maximally-tolerated dose (MTD). In the BET115521 monotherapy trial, ER+ breast cancer subjects with disease that progressed after multiple prior lines of therapy were enrolled. A planned interim futility analysis in this population was performed, and GSK stopped enrolment in this single agent cohort, based upon limited benefit.

BET inhibition and ER-targeted therapy have been demonstrated to target ER expression and change ER-dependent gene expression in preclinical models. A recent study demonstrated that BET inhibition leads to ER downregulation [Feng, 2014]. Furthermore, BET inhibition leads to effects independent of ER expression, such as downregulation of c-myc and BCL2, in a variety of preclinical models [Wyce, 2013; Mertz, 2011; Delmore, 2011]. These pathways have been demonstrated to be critical for endocrine resistance [McNeil, 2006; Miller, 2011; Planas-Silva, 2007; Chrzan, 2001]. In tamoxifen-resistant cells (a model of progressive ER+BC), a combination of BET inhibitor plus fulvestrant (which selectively targets the ER for proteasomal degradation) suppressed cell growth *in vitro* and induced tumor shrinkage *in vivo* [Feng, 2014]. Moreover, mouse xenograft models of ER+ disease demonstrated improved survival when animals were treated with the combination of GSK525762 and fulvestrant, versus vehicle or either agent alone (Figure 1).

Taken together, these preclinical data suggest a mechanism by which BET inhibitors and endocrine-targeted therapy may combine to provide synergistic benefit in HR+/HER2- BC.

Figure 1 ***In vivo* study of MCF-7 cell mouse xenograft model; overall survival is improved when GSK525762 is combined with fulvestrant (purple line), compared to either agent alone**



This study (201973) proposes to evaluate the combination of GSK525762, a potent inhibitor of the BET family of proteins, with fulvestrant, in women with HR+/HER2- BC. Both agents are inhibitors of distinct but convergent molecular mechanisms that are critical for growth and proliferation of breast cancer tumor cells. This is a combination Phase I and Phase II study; the objectives are to first identify a dose of GSK525762 that

may be combined safely with fulvestrant, followed by a Phase II study to identify clinical activity of the drugs when given in combination.

3. OBJECTIVE(S) AND ENDPOINT(S)

Phase I

With the implementation of amendment 06, Phase I of the study is closed to enrolment.

Objectives	Endpoints
Primary	
• To determine a recommended Phase 2 dose (RP2D) of GSK525762, when given in combination with fulvestrant, in women with advanced or metastatic estrogen receptor positive 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] data
Secondary	
• 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 the 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 CR plus PR plus stable disease [SD] rate), duration of response, and progression-free survival (PFS)
• To characterize the exposure to GSK525762 and fulvestrant, when given in combination.	• Concentrations of GSK525762, GSK525762 relevant metabolites and fulvestrant following administration in combination
Exploratory	
• 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	• Transcriptomic and/or protein changes in molecular markers of BET inhibition and HR signaling in tumor tissue
• 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.

Objectives	Endpoints
• 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 (TTG) predicted with the model parameters and relationship with clinical activity parameters.
• To evaluate the exposure response relationship between GSK525762 and/or fulvestrant exposure and safety and efficacy parameters. • To evaluate the effect of GSK525762 and fulvestrant, when given in combination, on symptoms and quality of life • 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	• Relationship between GSK525762 and/or fulvestrant exposure markers (e.g. dose, Cmin, Cmax), and safety/efficacy parameters. • Change from baseline in EORTC-QLQ-C30 and EORTC-QLQ-BR23 questionnaires. Changes from baseline in select items from the PRO-CTCAE • Targeted sequencing to determine correlation between ESR1 mutations and clinical response

Phase II

With the implementation of amendment 06, Phase II of the study is terminated.

Objectives	Endpoints
Primary	
• To evaluate the effect of treatment with GSK525762 and fulvestrant, when given in combination, on progression-free survival in women with advanced or metastatic HR+/HER2- BC	• Progression free survival (PFS), defined as the median time from the first dose of study treatment until objective tumor progression or death from any cause, whichever comes first
Secondary	
• To evaluate the effect of treatment with GSK525762 and fulvestrant, when given in combination in women with advanced or metastatic HR+/HER2- BC, on additional metrics of subject survival • To evaluate the clinical activity of GSK525762 and fulvestrant, when given in combination • To characterize the exposure to GSK525762, when given in combination with fulvestrant. • To characterize the exposure to fulvestrant when given alone or with GSK525762	• Overall survival (OS) • ORR, DCR • GSK525762 and metabolites concentrations following administration in combination with fulvestrant • Fulvestrant concentrations following administration alone or in combination with GSK525762

Objectives	Endpoints
Exploratory	
• 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
• To describe the kinetics of tumor growth in the presence or absence of GSK525762 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 (TTG) predicted with the model parameters and relationship with clinical activity parameters
• To evaluate the exposure response relationship between GSK525762 and/or fulvestrant exposure and safety and efficacy parameters • To evaluate the effect of GSK525762 and fulvestrant, when given in combination, on symptoms and quality of life • 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	• Relationship between GSK525762 and/or fulvestrant exposure markers (e.g. dose, Cmin, Cmax), and safety/efficacy parameters. • Change from baseline in EORTC-QLQ-C30 and EORTC-QLQ-BR23 questionnaires • Targeted sequencing to determine correlation between ESR1 mutations and clinical response

4. STUDY DESIGN

4.1. Overall Design

This study is a Phase I/II dose-escalation, expansion (Phase I) and randomized control study (Phase II) study with oral administration of GSK525762 in combination with fulvestrant in advanced or metastatic HR+HER2-BC subjects, who have disease that has progressed on prior treatment with at least one line of endocrine therapy.

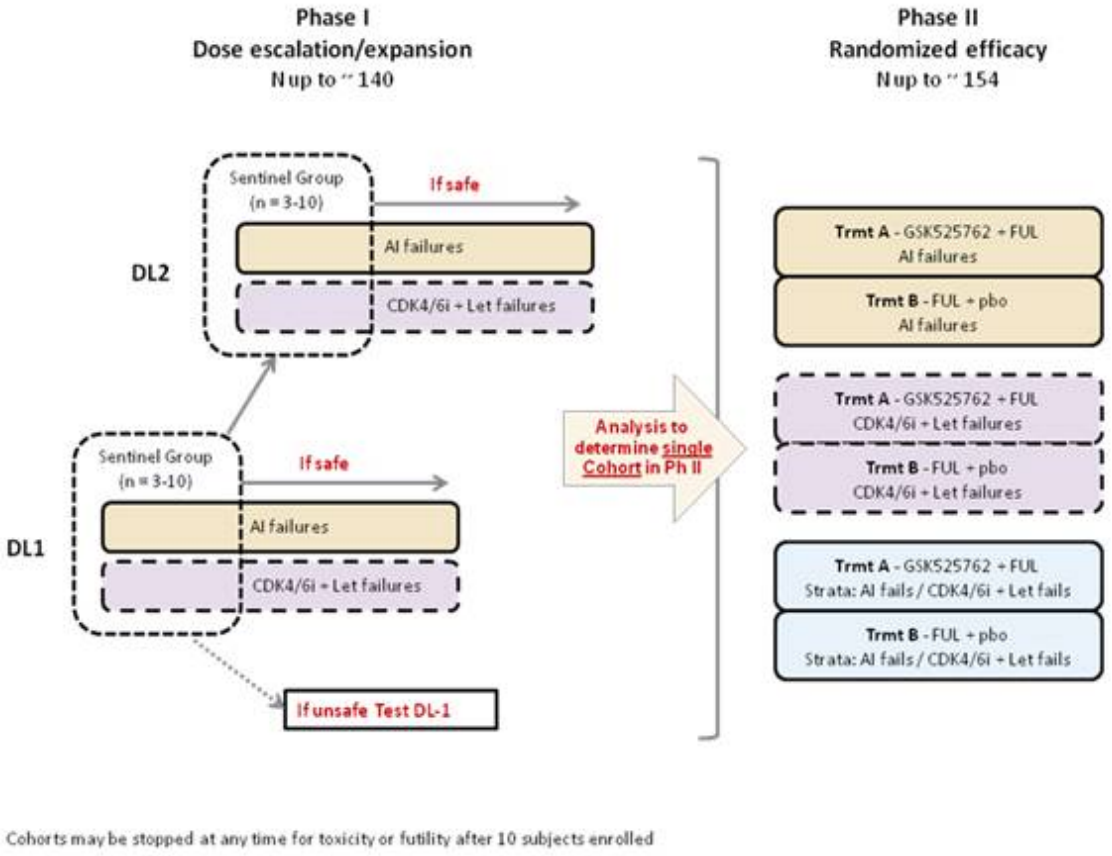
4.1.1. Original Overall Design (Protocols 01-04)

Phase I of the study is designed as parallel single arm treatment with GSK525762 in combination with fulvestrant in two distinct populations of HR+/HER2- breast cancer to determine a recommended Phase 2 dose RP2D based on safety, tolerability, pharmacokinetic, and efficacy profiles. [Changes have been made to this Phase, see changes below in Section 4.1.2]

Phase II of the study is designed as a randomized, double-blind, placebo-controlled cohort, the composition of which will be selected at the end of Phase I, based upon the totality of Phase I data. This cohort will compare the efficacy of GSK525762 in combination with fulvestrant versus fulvestrant with GSK525762-matched placebo in subjects with disease that progressed on anti-estrogen and/or one or more AIs, or failure

of a combination treatment with CDK4/6 inhibitor plus letrozole or a combination of both of these groups/patient populations (Figure 2).

Figure 2 Study Schematic



Phase I:

Phase I will study the safety, tolerability, PK, and efficacy of GSK525762 plus fulvestrant when administered in combination in up to two escalating dose levels (DLs). Eligible subjects must have advanced or metastatic HR+/HER2- BC that has been refractory to, or progressed despite, prior systemic therapy. The combination of GSK525762 plus fulvestrant will be evaluated in an open-label fashion in two separate populations of subjects (i.e., two cohorts). These cohorts will be evaluated at both DLs (see Inclusion and Exclusion criteria in Section 5.1 and Section 5.2 for full details):

- Subjects who have disease that has relapsed during treatment or within 12 months of completion of adjuvant therapy with an AI, OR disease that progressed during treatment with an AI for advanced/metastatic disease. Prior ovarian suppression and/or tamoxifen are allowed as long as the other criteria are met.
- Subjects who have disease that has progressed during treatment with the combination of a CDK4/6 inhibitor (e.g., palbociclib) plus letrozole for advanced

or metastatic disease. Prior ovarian suppression and/or tamoxifen are allowed as long as the other criteria are met.

Documented progression on the last line of systemic anti-cancer therapy is required.

Phase I will follow a modified toxicity probability interval (mTPI) design. The design assumes (i) approximately 30 subjects will complete the dose-limiting toxicity (DLT) evaluation period and (ii) the true underlying toxicity rate for GSK525762 in combination with fulvestrant falls within the range from 25% to 35% and centered at 30%.

Subjects in DL1 will begin dosing with fulvestrant at the approved dose, plus GSK525762 at one dose level lower than the single-agent RP2D. Subjects will be enrolled into one of two possible cohorts, based on their prior treatment history, as defined above. A sentinel group (comprising subjects enrolled in both cohorts) of at least 3 and up to 10 subjects will be evaluated for safety. If the DLT rate of the DL1 sentinel group does not exceed the maximum permitted toxicity rate as defined by the mTPI, the following will occur in parallel:

- At DL1, up to 35 subjects will be enrolled into each cohort
- Evaluation of DL2

Subjects in DL2 will begin dosing with fulvestrant at the approved dose, plus GSK525762 at the single agent RP2D. Subjects will be enrolled into one of two possible cohorts, based on their prior treatment history, as defined above. A sentinel group (comprising subjects enrolled in both cohorts) of at least 3 and up to 10 subjects will be evaluated for safety. During enrolment of the DL2 sentinel group, the enrolment for DL1 will be temporarily closed. After completing the enrolment for the sentinel group of DL2, the enrolment for DL1 will be re-opened and the enrolment for DL2 will be temporarily closed while waiting for the 28 days DLT observation period to be completed for all subjects.

If the DLT rate of the DL2 sentinel group does not exceed the maximum permitted toxicity rate, enrolment for DL2 will be re-opened and the enrolment for DL1 will be temporarily closed **until DL2 enrols the same number of subjects as DL1**. After that, both DL1 and DL2 will be open to enrolment, and subjects will be assigned 1:1 to either DL1 or DL2 until one or the other dose level is filled or terminated. All subjects would then be enrolled at the remaining dose level. Refer to Section 4.2.3.2 for details of dose level and cohort selection.

Each cohort (two at each DL) may enroll up to 35 subjects, for a total of approximately 70 subjects enrolled at each DL. The total number of subjects enrolled into each cohort may vary, as interim analyses for safety and efficacy may terminate any cohort if the DLT rate exceeds the maximum permitted toxicity rate per the mTPI, or if the efficacy rate does not exceed the historical overall response rate (ORR).

If the DLT rate of the sentinel group in DL1 exceeds the maximum permitted toxicity rate as defined by the mTPI, then a lower dose level (DL-1) will be evaluated. If the DLT rate of the sentinel group in DL2 exceeds the maximum permitted toxicity rate as

defined by the mTPI, then additional subjects will not be enrolled at DL2, and all subjects will be enrolled at DL1.

Subjects must have disease that is evaluable for response. The primary endpoints of Phase I of the study are safety and clinical response, based on ORR. Additional efficacy data, including PFS and OS, will be collected from all subjects treated in Phase I. The totality of data, including safety/tolerability, PK, and efficacy, will be used to determine whether to proceed to Phase II, and which cohort and dose to be carried forward into Phase II.

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. Enrolment into the study is now closed as interim data failed to demonstrate meaningful clinical benefit in this patient population.

With the implementation of Amendment 06, specific assessments and collection of survival follow-up data will no longer be required. Please see Section 7.1for further details. The study will conclude when the last subject has completed/discontinued study treatment and completed the end of treatment visit. There will be no Phase II.

Phase II:

Phase II is a randomized, double-blind, placebo-controlled study that will explore the clinical activity of GSK525762 and fulvestrant when given in combination, to subjects with advanced or metastatic HR+/HER2- BC. The primary endpoint of Phase II is PFS.

Phase II will be composed of one cohort, the composition and the dose of which will be decided based on the totality of the data at the end of Phase I. If any of the prior treatment history-specific cohorts in Phase I are terminated early for toxicity or lack of efficacy at any dose, enrolment of subjects with those prior therapies at that dose will not be carried forward into Phase II. Phase II will enrol subjects who have disease that has progressed after prior therapy with:

- AIs alone (either in the setting of primary metastatic disease or on-treatment/within 12 months of discontinuing adjuvant endocrine therapy), OR
- CDK4/6 inhibitor plus letrozole, OR
- Either AI therapy OR CDK4/6 inhibitor plus letrozole. If both cohorts are permitted to enroll in Phase II, randomization will be stratified by prior CDK4/6 inhibitor-based therapy (i.e., CDK4/6 inhibitor-naïve versus CDK4/6 inhibitor-exposed) and corresponding stratified analysis will be provided at interim and final analyses.

Eligible subjects will be randomized 1:1 to receive GSK525762 plus fulvestrant (Arm A), or fulvestrant plus GSK525762-matched placebo (Arm B), in a double-blinded fashion. Note that subjects may have received up to one line of cytotoxic chemotherapy in the advanced/metastatic setting. In addition, subjects enrolled in the CDK4/6 inhibitor plus letrozole cohort may have failed therapy with any number of lines of anti-estrogens and/or AIs. Subjects will be treated until progression, toxicity, or withdrawal of consent.

The primary endpoint of this Phase of the study will be progression free survival (PFS); comparison of primary and secondary endpoints will be performed between the investigational and control arms.

4.1.2. Revised Overall Design (Protocol Amendment 05)

While the overall study goals and design remain same, changes have been made to Phase I of the study to address to emerging data and intended to better define the patient population most likely to benefit from combination treatment of molibresib plus fulvestrant. The following are to be noted:

1. DL1 Cohort 1 (60 mg, AI-failures) will complete enrolment to 35 subjects as under amendment 4

2. DL1 Cohort 2 (60 mg, CDK4/6 inhibitor plus AI failure) – change in inclusion criteria and to the number of subjects to be enrolled is detailed below in Section 4.1.2.1.

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.

4. Phase II design remains unchanged – as originally stated, this Phase of the study will be redesigned based after analysis of Phase I data.

4.1.2.1. Change to DL1 Cohort 2:

- 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;
    - 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.
    - 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.
    - The total number of subjects enrolled into this cohort will be approximately 75.
    - Prior ovarian suppression and/or tamoxifen are allowed as long as the other criteria are met.

This requirement is based on emerging data and intended to better define the patient population most likely to benefit from combination treatment. The required number of subjects is described in Section 9.2.

4.1.3. Type and Number of Subjects

All subjects enrolled in this study will have a diagnosis of advanced or metastatic HR+/HER2- BC, that has progressed on prior treatment with at least one line of therapy,

or which has progressed while on or within 12 months of discontinuing adjuvant endocrine therapy. Cohort 2 is modified to include a minimum of 48 subjects who have progressed after greater than or equal to 12 months of a CDK4/6 inhibitor (e.g., palbociclib) plus AI for advanced or metastatic disease with either measurable disease (32 subjects) or bone only disease (16 subjects).

Approximately 140 subjects will be enrolled in Phase I, and approximately 154 subjects total will be enrolled in Phase II. Further details of the type and number of subjects are described in Section 4.2.1 and Section 4.4.1.

4.2. Phase I

The primary objective of Phase I is to determine a 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.

As described in Section 4.6 and shown in Figure 2, dosing will begin at DL1. Subjects in DL1 will begin dosing with fulvestrant at the approved dose, plus GSK525762 at one dose level lower than the single-agent RP2D (i.e., 60 mg of GSK525762 orally once daily and 500 mg of fulvestrant intramuscularly (IM) on Days 1, 15, and 29 of cycle 1, and monthly thereafter). Subjects will be enrolled into one of two possible cohorts, based on their prior treatment history as described in Section 4.2.1. Dose escalation decisions will be made based upon data from a small sentinel group pooled from across both cohorts. Once three subjects (irrespective of cohort) are enrolled at DL1, a modified toxicity probability interval table (Figure 3) will be used to determine whether to dose-escalate, dose-deescalate, or enroll additional subjects at DL1. If additional subjects are required to make a dose escalation decision, then subjects will be enrolled in groups of approximately three to collect additional safety data. Up to 10 subjects may be used for dose escalation decision making. If the DLT rate of the DL1 sentinel group does not exceed the maximum permitted toxicity rate as defined by the mTPI, then two events will occur in parallel:

- At DL1, additional subjects will be enrolled into each cohort, up to 35 subjects in each cohort as described below
- Evaluation of DL2 will begin

Subjects in DL2 will begin dosing with fulvestrant at the approved dose, plus GSK525762 at 80 mg. Subjects will be enrolled into one of two possible cohorts, based on their prior treatment history as described in Section 4.2.1. As in DL1, a sentinel group of at least 3 and up to 10 subjects will be evaluated for safety. If the DLT rate of the DL2 sentinel group does not exceed the maximum permitted toxicity rate as defined by the mTPI, then up to 35 subjects will be enrolled into each cohort.

Each cohort (two at each DL) may enroll up to 35 subjects, for a total of approximately 70 subjects enrolled at each dose level. The total number of subjects enrolled into each cohort may vary, as interim analyses for safety and efficacy may terminate any cohort if the DLT rate exceeds the maximum permitted toxicity rate per the mTPI, or if the efficacy rate does not exceed the historical overall response rate (ORR). Each dose level

may be over-enrolled in order to ensure that an adequate number of subjects complete the cohort in a timely manner.

4.2.1. Type and Number of Subjects in Phase I

In Phase I, subjects must have a diagnosis of relapsed or refractory, advanced or metastatic, histologically or cytologically confirmed HR+/HER2- BC. Full details of inclusion and exclusion criteria may be found in Section 5.1 and Section 5.2. See Protocol Section 4.1.2 for details on the type and number of subjects in Phase I.

4.2.2. Treatment Arms and Duration

In Phase I, all subjects will receive GSK525762 in combination with fulvestrant. Subjects will begin combination therapy and will continue until unacceptable toxicity, progression of disease, or withdrawal of consent. Enrolment into DL2 has been discontinued. See Protocol Section 4.1.2 for the current design. The total duration of study will depend on recruitment rates, withdrawals due to toxicity or progression, and the timing of subjects' duration on study, with an estimate of 15 months for Phase I, and 16 months for Phase II.

In Phase I, subjects in the sentinel groups will be replaced if they are unable to receive at least 75% of the scheduled doses (of both agents, at the intended strength) during the 28-day DLT observation period for reasons other than toxicity. Once the sentinel groups have cleared, all further subjects will not be replaced if they discontinue prematurely.

4.2.3. Dose Selection

4.2.3.1. Planned Dose Levels

The projected DLs of GSK525762 are 60 mg and 80 mg administered orally once daily. DL2 (80 mg) has been discontinued. If unacceptable toxicity is observed at the 60 mg DL, then 40 mg once daily may be explored (DL-1). The projected DL of fulvestrant is the approved dose regimen of 500 mg intramuscularly (IM) on Days 1, 15, and 29 of cycle 1, and monthly thereafter.

Additional doses and schedules may be explored based on emerging safety, PK, and PD data. No doses will be explored beyond 100 mg GSK525762 or 500 mg (IM) fulvestrant, these doses that are considered to be the Maximum Feasible Dose (MFD), unless emerging PK data demonstrate reduced exposure of either drug in combination compared to single agent.

4.2.3.2. Dose Level & Cohort Selection

In Phase I, subjects will be enrolled into one of two cohorts based on their most recent prior treatment history, as described in Section 4.2.1. Once three evaluable subjects (total, irrespective of cohort) have cleared the DLT evaluation period (refer to Section 4.2.3.4 for definitions of 'evaluable' and for DLT details), then an mTPI method (Section 4.2.3.3) 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). Additional subjects, up to 10 total evaluable, 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.

If DL1 is found to exceed the pre-specified toxicity, then DL-1 will be evaluated. If DL2 is found to exceed the pre-specified toxicity, then additional enrolment in DL2 will cease and all subjects will be enrolled to cohorts at DL1.

DL2 (80 mg) is discontinued.

4.2.3.3. Dose Escalation & Cohort Safety Decisions

A data review team, consisting (at a minimum) of the investigator(s), Medical Monitors, safety physician, pharmacokineticist, clinical representatives, and statistician will be responsible for determining whether dose escalation and expansion during Phase I should continue as planned according to the mTPI design rules together with the predicted DLT rates at all DLs. Prior to the dose escalation decision, the data review team will review available relevant data on all AEs including non-DLT toxicities, laboratory assessments and other safety evaluations, as well as any available PK data as described in the Dose Escalation Plan. Quality control of critical safety data will also be described in the Dose Escalation Plan, which includes ongoing study monitoring visits, Sponsor review of the clinical database, and confirmation by site investigators and/or delegate that the data is accurate and complete. The dose-escalation decision and rationale for each cohort will be discussed with investigators during teleconference(s). The dose decision and rationale for each cohort will be documented in writing with copies maintained at each study site and in the master study files at GlaxoSmithKline (GSK).

A modified Toxicity Probability Interval (mTPI) design will be implemented (Figure 3) [Ji, 2010]. The mTPI decision rule will be followed for monitoring safety until 35 subjects have been assigned at the same dose

The design assumes (i) Approximately 30 subjects will complete the DLT evaluation period and (ii) the true underlying toxicity rate for GSK525762 in combination with fulvestrant falls within the range from 25% to 35% and centered at 30%. The monitoring rules guiding dose escalation are provided in Figure 3. Columns provide the numbers of subjects treated at the current dose level, and rows provide the corresponding numbers of subjects experiencing toxicity. The entries of the table are dose-finding decisions (i.e., E, S, and D) representing escalating the dose, staying at the same dose, and de-escalating the dose. If the current dose is at the highest dose level and the decision is E, it indicates that the highest dose level is below MTD and the next subject(s) will be treated at the same dose level. In addition, decision U means that the current dose level is unacceptable because of high toxicity and should be excluded from the trial. For example, when one of three subjects experiences toxicity, the decision can be located at row 1 and column 3, which is S – to stay at the current dose level. Consequently, the next cohort of subjects will be treated at the same dose level currently being used. If zero of three subjects experiences toxicity, the decision is at row 0 and column 3, which is E – to escalate if there is higher available dose otherwise stop dose escalation if there are 6 evaluable

subjects on the current dose. Thus, the next cohort of subjects will be treated at the next-higher dose level. If three of three subjects experiences toxicity, the decision is DU – to de-escalate to the next-lower dose level and exclude the current dose from the trial, because the high toxicity level is unacceptable.

Figure 3 Dose-finding spreadsheet of the modified toxicity probability interval (mTPI) method

Number of dose limiting toxicities (DLT's)	Number of patients treated at current dose																													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
2		DU	D	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
3			DU	DU	D	S	S	S	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
4				DU	DU	DU	D	D	S	S	S	S	S	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E
5					DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	E	E	E	E	E
6						DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	E
7							DU	DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
8								DU	DU	DU	DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	S
9									DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S	S	S	S	S	S	S	S	S
10										DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S
11											DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S	S	S	S	S
12												DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S
13													DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S
14														DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
15															DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
16																DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
17																	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
18																		DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
19																			DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
20																				DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
21																					DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
22																						DU	DU	DU	DU	DU	DU	DU	DU	DU
23																							DU	DU	DU	DU	DU	DU	DU	DU
24																								DU	DU	DU	DU	DU	DU	DU
25																									DU	DU	DU	DU	DU	DU
26																										DU	DU	DU	DU	DU
27																											DU	DU	DU	DU
28																												DU	DU	DU
29																													DU	DU
30																														DU

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
U = The current dose is unacceptably toxic

MTD = 30%
Sample Size = 30
Epsilon1 = 0.05
Epsilon2 = 0.05

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.

4.2.3.4. Dose-Limiting Toxicity Definition

The mTPI decision rules are based on the number of DLTs; an event will be considered a DLT if it occurs within the first 28 days of treatment and meets at least one of the criteria listed in

Table 1, unless it can be clearly established that the event is unrelated to treatment.

Table 1 Dose-Limiting Toxicity Criteria

Toxicity	DLT Definition
Hematologic	• Grade 3 or greater neutropenia for ≥5 days • Febrile neutropenia • Grade 4 anemia of any duration • Grade 4 thrombocytopenia of any duration or Grade 3 thrombocytopenia with bleeding
Non-hematologic	• Alanine aminotransferase (ALT) >3x upper limit of normal (ULN) + bilirubin ≥2xULN (>35% direct) or ALT between 3-5 X ULN with bilirubin <2xULN but with hepatitis symptoms or rash (See Section 5.4.1 for Liver Stopping Criteria) • Grade 3 nausea, vomiting or diarrhea that does not improve within 72 h despite appropriate supportive treatment(s) • Grade 4 nausea, vomiting, or diarrhea • Grade 3 hypertension[a] (uncontrolled despite addition of up to 2 antihypertensive medications) • Grade 4 hypertension • Other Grade 3 or greater clinically significant non-hematologic toxicity (including QT duration corrected for heart rate by Fridericia's formula (QTcF) except toxicities listed in Section 4.2.3.5. • Ejection fraction < lower limit of normal (LLN) with an absolute decrease of >10%from baseline
Other	• Inability to receive at least 75% of scheduled doses in the DLT observation period due to drug-related toxicity, or any toxicity which requires permanent discontinuation of investigational agent(s) during the DLT observation period[b] • Grade 2 or higher toxicity that occurs beyond 28 days which in the judgment of the investigator and Medical Monitor is considered to be a DLT

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

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

Refer to Appendix 2 for management of selected toxicities.

4.2.3.5. Non-Limiting Toxicities

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

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

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

4.2.3.6. Maximum Dose Increment

The pre-planned dose levels are described in Section 4.2.3.1. Only GSK525762 will be dose-escalated at each dose escalation step.

4.2.3.7. Alternative Dosing Schedules

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

Schedules that incorporate a recovery period for GSK525762 may be explored (e.g., 2 weeks on, 1 week off). This approach will be considered if the safety and PK data suggest that a therapeutic exposure for GSK525762 cannot be achieved using the initial schedule without excessive toxicity. The starting dose for the alternate schedule will be the highest completed dose level with the initial schedule. Escalation can then proceed as described in Section 4.2.3.2.

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

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

4.2.3.8. Intra-Subject Dose Escalation

During Phase I, intra-subject dose escalation will not be permitted. Upon completion of Phase I, any subject treated below the RP2D may be dose-escalated to a higher cleared dose level (not to exceed the RP2D) after discussion with the medical monitor. Refer to Section 4.3 for more details. After discontinuation of DL2 subjects will not automatically be reduced to DL1 if they have a favourable risk/benefit profile.

4.2.4. Data Review

An independent data monitoring committee (IDMC) will not be implemented in Phase I of the study, as 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 (as described in Section 4.3).

4.2.5. Statistical Analysis

In Phase I, Bayesian methods will be used to investigate clinical activity (defined as ORR). This design also allows the study to be frequently monitored with the constraint of both Type I and Type II error rates and also allows the enrollment to be halted due to futility for a given cohort. For details of the design and decision rules, refer to Section 9.4.

Inference stemming from the Bayesian models of efficacy in subjects harboring HR+/HER2- BC is intended to inform decision making. Actual decisions will depend on the totality of the efficacy and safety data. The decision to terminate any cohort will not depend solely on the results of the statistical model but will take all factors into account, including the results of the model, safety, tolerability, and PK data. In some cases, additional subjects in a cohort may be enrolled even if the model suggests a low likelihood of activity.

The safety and efficacy of GSK525762 in combination with fulvestrant will be monitored by frequent interim analyses. After at least 10 evaluable subjects are available in a cohort, the first interim data review on efficacy may take place. The data review on safety using mTPI method can be conducted at any time. Please see details in Section 9.4.

Cohorts may be discontinued for toxicity or lack of efficacy as described below:

4.2.5.1. Safety Analysis

At each safety interim analysis, the number of DLTs, number of evaluable subjects, and the observed DLT rate will be reported for each cohort. The mTPI decision rule will be used for monitoring safety until 30 subjects have been assigned at the same dose, at which time further enrolment will halt. According to mTPI decision rules (Figure 3), once D or DU decision is met or observed DLT rate ≥0.33 for any cohort, the enrolment for that cohort will be stopped.

4.2.5.2. Futility Analysis

When at least 10 evaluable subjects are available in a cohort, the first interim data review on efficacy may take place for that expansion cohort. After that, interim analysis may be conducted after every 5 evaluable subjects become available. For each cohort, the enrolment for that cohort may be stopped due to futility if the Bayesian posterior

probability that the confirmed response rate ≥25% in Cohort 1 (AI Failure) or ≥20% in Cohort 2 (CDK4/6+AI Failure) (target) is small (e.g., less than a 10% chance). For details, please see Section 9.4.

Refer to Appendix 3 for a discussion of the response assumptions used in the statistical model.

4.3. Decision to Proceed to Phase II

With the implementation of amendment 06, Phase II of the study is terminated.

The decision to proceed to Phase II will be based on totality of data including safety, efficacy, PK and PD data.

After RP2D is established, any subjects still receiving therapy with GSK525762 and fulvestrant may continue receiving drug(s) until progression, death, withdrawal of consent, or unacceptable toxicity, as described in Section 5.4. Any subject treated below the RP2D may be dose-escalated to a higher dose level (not to exceed the RP2D). Clinic visits and efficacy analysis should continue as described in the Time and Events Table. Refer to Section 9.1.2 for statistical consideration of dose/cohort selection.

4.3.1. Phase II Dose Selection

Upon completion of Phase I, all available data (including data from subjects who prematurely discontinue therapy) will be compiled and summarized. The dose(s) taken into Phase II will be based upon the totality of data from Phase I, including safety, tolerability, efficacy, and PK data.

4.3.2. Phase II Cohort Selection

The choice of cohort to be further studied in Phase II will depend on the safety and efficacy data from Phase I. If any of the prior treatment history-specific cohorts in Phase I are terminated early for toxicity or lack of efficacy (as described in Section 4.2.3.3), enrolment of subjects with those prior therapies will not be carried forward into Phase II.

Based on results from Phase I, Phase II will enrol subjects who have disease that has progressed after prior therapy with:

- AIs alone (either in the setting of primary metastatic disease or on-treatment/within 12 months of discontinuing adjuvant endocrine therapy), OR
- CDK4/6 inhibitor plus AI, OR
- either AI therapy OR CDK4/6 inhibitor plus AI. If both cohorts are permitted to enroll in Phase II, randomization will be stratified by prior CDK4/6 inhibitor-based therapy (i.e., CDK4/6 inhibitor-naïve versus CDK4/6 inhibitor-exposed) and corresponding stratified analysis will be provided at interim and final analyses.

4.4. Phase II Prior Treatment History Specific Cohorts

Phase II is a randomized, placebo-controlled study of GSK525762 plus fulvestrant compared to fulvestrant with GSK525762-matched placebo for subjects with HR+/HER2- BC who have failed prior treatment with at least one line of endocrine-based therapy. The primary endpoint is PFS for both groups, with a goal of doubling PFS (i.e., a hazard ratio of 0.5). Phase II will be redesigned based on the results for Phase I and the emerging data from literature.

4.4.1. Type and Number of Subjects

Phase II will be comprised of one cohort; the specific composition of this cohort will depend on the totality of data from Phase I of the study as described in Section 4.3. Subjects must have a disease that did not respond to, or that progressed after, at least one line of prior therapy. Refer to Section 4.3 for details of prior therapy and composition of the cohorts.

Refer to Section 9.2.1.2 for the statistical rationale for the number of subjects to be enrolled.

In Phase II, subjects will not be replaced if they prematurely discontinue therapy.

4.4.2. Treatment Arms and Duration

Approximately 154 subjects will be enrolled in Phase II of the study. The total duration of study will depend on recruitment rates, withdrawals due to toxicity or progression, and the timing of subjects' duration on study, with an estimate of 16 months for Phase II.

4.4.3. Dose Selection

Subjects will start dosing on Day 1 with the dose and schedule identified as the RP2D in Phase I of the study. The final dose and regimen for Phase II will be decided upon completion of Phase I as described in Section 4.3.

4.4.4. Group Assignments

Refer to Section 4.3.2 for details of the cohort that may enrol in Phase II. The eligible cohort will be selected at the end of Phase I, and the rationale for selection will be communicated to sites in writing.

4.4.5. Statistical Design

In Phase II, the primary goal is to demonstrate a clinically meaningful improvement in PFS when GSK525762 versus placebo is added to fulvestrant therapy. For this study, "clinically meaningful" is defined as a hazard ratio (HR) of 0.5, indicating that the combination therapy doubles the PFS relative to the comparator arm. A planned interim analysis will be performed when 45 subjects enrolled in Phase II have progressed or died; the study may be stopped at the time of interim analysis for safety as well as for futility or efficacy. Refer to Section 9.4.8.2 for details of the statistical analysis and to Section 9.4.10 for the explanation of the simulation.

4.4.6. Data Review

An IDMC will be utilized in Phase II of this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review will be described in the charter.

4.5. Design Justification

Given the unmet medical need of relapsed/refractory advanced HR+/HER2- BC, a Phase I/II study (201973) is proposed. The study comprises an open-label, single arm Phase I, followed by a randomized, double-blind, placebo-controlled Phase II.

4.5.1. Phase I

Phase I is a dose escalation/expansion study to determine the R2PD, whether to proceed to Phase II, and which cohort (defined by different lines of prior therapy) should be further studied in the randomized, blinded, controlled Phase II. Decisions will be based on both efficacy as well as safety.

Efficacy will be monitored via frequent interim analyses. Bayesian designs that allow the trial to be frequently monitored with the constraint of both Type I and Type II error rates will be used. Clinical response will be defined as confirmed ORR, per standard evaluation criteria (see Appendix 7 for definitions of response assessments and criteria). Bayesian predictive adaptive design [Lee, 2008] will be used to investigate the clinical activity in each cohort. The criteria will be based on a clinically ineffective response rate of 10% and 5% in Cohort 1 (AI Failure) and Cohort 2 (CDK4/6+AI Failure), respectively versus a clinically meaningful response rate 25% and 20% in Cohort 1 (AI Failure) and Cohort 2 (CDK4/6+AI Failure), respectively; the rationales for these response assumptions are described in Appendix 3.

Dose escalation/de-escalation decisions will be based primarily on the mTPI design [Ji, 2010], a well-validated method for identifying the MTD of oncology therapeutics.

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. Enrolment into the study is now closed.

With the implementation of Amendment 06, specific assessments and collection of survival follow-up data will no longer be required. Please see Section 7.1 for further details. The study will conclude when the last subject has completed/discontinued study treatment and completed the end of treatment visit.

4.5.2. Phase II

Phase II is a randomized, double-blind, placebo-controlled study that will explore the clinical activity of GSK525762 and fulvestrant when given in combination to subjects

with advanced or metastatic HR+/HER2- BC, compared to control. One interim analysis will be performed once 45 events have occurred. Refer to Section 9.4.10 for details of statistical modeling and to Appendix 3 for rationale for clinical response assumptions.

4.6. Dose Justification

GSK525762 and fulvestrant have not been previously administered in combination in subjects with cancer. Both have been administered as single agents to women with HR+/HER2- BC, and fulvestrant is currently approved as a single agent and in combination with other agents to treat HR+/HER2- BC.

4.6.1. Starting Doses

GSK525762:

A Phase I/II study (BET115521) with GSK525762 (as a single agent) is currently underway in subjects with advanced solid tumors, including ER+BC. Doses of 2 to 100 mg QD and doses of 20 mg and 30 mg BID have been evaluated. The RP2D was determined to be 80 mg QD with GSK525762 free base amorphous tablet, or 75 mg with the besylate salt tablet based on available tablet strengths. Section 5.3 of the GSK525762 Investigator's Brochure [GlaxoSmithKline Document Number 2011N113741_07] details the clinical experience to date with GSK525762 including clinical safety data in the solid tumor population up to 100 mg once daily and in the hematologic malignancy population up to 120 mg once daily.

The initial dose of GSK525762 administered in Phase I of this study will be reduced to 60 mg of the besylate salt tablet, which represents a 20% dose reduction from the single-agent RP2D. There were no dose limiting toxicities (DLT) observed at the 60 mg dose administered to subjects with solid tumors in the first time in human (FTIH) study BET115521 [GlaxoSmithKline Document Number 2011N113741_07].

Fulvestrant:

For fulvestrant, doses ranging from 125 to 500 mg have been administered to subjects with ER+BC. Doses of 250 mg and 500 mg have been studied extensively in Phase 3 studies, and 500 mg was chosen based on superior clinical activity (fulvestrant package insert, Section 14). The currently approved dose of fulvestrant is 500 mg intramuscularly (IM) on days 1, 15, and 29 of cycle 1, and then monthly thereafter. This is the approved dose for fulvestrant administered as a single agent, as well as in combination with palbociclib. Dose reductions (to 250 mg administered on the same schedule) are stipulated for subjects with underlying hepatic impairment. While the inclusion/exclusion criteria (Section 5.1 and Section 5.2) exclude subjects with significant liver dysfunction at baseline, emerging toxicity may warrant a dose reduction as described in Appendix 2.

For Phase I and Phase II of this study, fulvestrant will be administered at the 500 mg dose strength as detailed in the package insert. Refer to Section 6.1 of this protocol or Section 2.3 of the package insert for details of administration.

4.6.2. Drug-Drug Interactions

The risk of a pharmacokinetic drug-drug interaction between GSK525762 and fulvestrant is low.

Drugs as victim: GSK525762 appears to be primarily metabolized by cytochrome P450 (CYP) 3A4 and does not appear to be metabolized by CYP2C8, CYP2C9, or CYP2C19. Metabolism of fulvestrant appears to involve combinations of a number of possible biotranformation pathways analogous to those of endogenous steroids, including oxidation, conjugation with glucuronic acid and/or sulphate, and aromatic hydroxylation. In vitro studies suggest that CYP3A4 is the only CYP isoenzyme involved in the oxidation of fulvestrant; however, the relative contribution of CYP enzymes *in vivo* is not known. Drug-drug interaction studies using inducers and inhibitors of CYP3A4 (rifampin and ketoconazole, respectively) did not alter fulvestrant pharmacokinetics.

Drugs as perpetrator: The potential for GSK525762 to inhibit the clearance of possible co-medications metabolized by major CYP enzymes was considered to be low. An in vitro study in human liver microsomes with clinically-relevant substrates of CYPs 2B6, 2C8 and 3A4 revealed that GSK525762 did not directly inhibit these enzymes (IC50 >100 μM), nor was there any metabolism-dependent inhibition. GSK525762 did not activate the human Pregnane X receptor (hPXR) in an in vitro assay (EC50 >50 μM); although based on in vitro hepatocyte and repeat dose clinical pharmacokinetic data, GSK525762 has the potential to induce CYP3A4.

Based on *in vitro* studies, fulvestrant is not an inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. Co-administration of fulvestrant with midazolam, a sensitive substrate of CYP3A4, did not demonstrate any effect of fulvestrant administration on CYP3A4 activity.

GSK525762 is a substrate for both breast cancer resistance protein (BCRP) and p-glycoprotein (Pgp), whilst fulvestrant is not a substrate for either transporter. Neither agent appears to inhibit BCRP nor Pgp at doses achieved in clinical studies.

4.6.3. Overlapping Toxicities

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

In summary, the likelihood that GSK525762 or fulvestrant will have an effect on the PK of the other is low. The AE profiles of both agents, however, contain some common toxicities. Therefore, to reduce the risk of toxicity and assess the safety and tolerability of the combination, the starting dose of GSK525762 will be reduced to 60 mg QD in combination with the approved dose of fulvestrant. Lower exposures (either via lower dose or intermittent dosing) may be evaluated if 60 mg QD proves to yield unacceptable toxicity in Phase I.

4.7. Benefit: Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK525762 can be found in the Investigator's Brochure (IB). Summaries of findings from both clinical and non-clinical studies conducted with fulvestrant can be found in the package insert. The following section outlines the risk assessment and mitigation strategy for this protocol.

4.7.1. Risk Assessment

The toxicities listed below are a summary of those most likely to be observed in clinical practice, or are of special interest. For a full list of predicted and observed toxicities, refer to the GSK525762 IB GlaxoSmithKline Document Number 2011N113741_07 and the fulvestrant package insert.

4.7.1.1. Predicted Overlapping Toxicities

4.7.1.1.1. Gastrointestinal Safety Findings

Fulvestrant: As described in the fulvestrant package insert (Section 6.1), in a study comparing fulvestrant at 500 mg and 250 mg, some of the most commonly reported adverse effects per treatment arm were gastrointestinal, including nausea (9.7%, 13.6%) vomiting (6.1%, 5.6%), constipation (5%, 3.5%), and anorexia (6.1%, 3.7%).

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

Monitoring and Management: During clinical studies, medical history, physical examination (including weight) and clinical laboratory assessments will be used to identify and assess toxicity in the GI tract. Management guidelines are included in the protocol for gastrointestinal toxicity (Appendix 2). In the event of clinically significant toxicity, treatment will be withheld, and supportive therapy provided according to standard medical practice.

4.7.1.1.2. Hepatic Safety Findings

Fulvestrant: As described in the fulvestrant package insert (Section 6.1), fulvestrant may cause liver enzyme abnormalities in a non-dose-dependent fashion. In the pooled safety population of 1127 subjects from clinical trials comparing fulvestrant 250 mg versus fulvestrant 500 mg, increases in either aspartate aminotransferase (AST), ALT, or alkaline phosphatise were observed in >15% of subjects. Grade 3-4 increases were rarer,

occurring in 1-2% of subjects. Hyperbilirubinemia was not reported as a common adverse event in clinical trials of fulvestrant.

GSK525762: In non-clinical animal studies, non-adverse liver changes were observed in rats, mice and dogs including increases in bilirubin levels in rats, increased bile acids in rats and mice and transient, reversible increased in AST and/or ALT in rats and dogs. Hepatocellular necrosis was observed in a single rat at a non-tolerated dose. In the BET115521 clinical trial, liver effects have been noted. Cases of liver events meeting the definition of severe liver injury based on liver chemistries (ALT ≥3X ULN and Bilirubin ≥2X ULN) have been reported in study BET115521. Additional complicating factors were reported for these cases (e.g. liver metastasis and sepsis) with liver enzymes trending towards normal levels upon stopping GSK525762. Drug related elevated blood bilirubin was reported in 24%, AST elevation was reported in 11%, and ALT elevation was reported in 8% of subjects. These drug related hepatic toxicities were predominantly Grades 1 and 2; 7% reported Grade 3 and <1% reported Grade 4 blood bilirubin increased and 2% of subjects reported Grade 3 AST increase. There were no Grade 4 ALT increases noted.

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

4.7.1.1.3. Hematopoietic Safety Findings

Fulvestrant: As described in the fulvestrant package insert (Section 6.1), fulvestrant was associated with anemia in 4-5% of subjects; approximately 14% of subjects experienced some adverse reaction related to the heme or lymphatic system. In addition, subjects with thrombocytopenia or other coagulopathies are at increased risk of adverse events, as fulvestrant is administered via IM injection, which could lead to intramuscular hematoma in subjects with impaired thrombosis and/or coagulation.

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

In the BET115521 clinical trial, thrombocytopenia was observed, primarily at higher dose levels. Thrombocytopenia was only noted after more than a week of continuous dosing, and platelet counts recovered after cessation of the drug. Refer to the GSK525762 IB for full details. Drug related thrombocytopenia was reported in 59%, anemia was reported in 29%, international normalized ratio increased was reported in 14%, prothrombin time prolonged in 12% and coagulation factor VII level decreased in 10% of subjects. These AEs were mainly Grade 1 or 2; with Grade 3 thrombocytopenia reported in 22%, Grade 3 anemia reported in 12% and Grade 3 factor VII decrease in 4%

of subjects. Grade 4 thromobocytopenia was reported in 16%, anaemia in 1% and factor VII decrease in 4% of subjects.

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

Monitoring and Management: Inclusion/exclusion criteria will require appropriate baseline hematologic and coagulation values prior to enrolment. Subjects will undergo frequent complete blood count (CBC) measurements, and management guidelines (Appendix 2) are included in the protocol to guide dose interruption/reduction decisions.

4.7.1.1.4. Reproductive Safety Findings

Fulvestrant: As described in the fulvestrant package insert (Section 5.3 and Section 8.1), fulvestrant can cause fetal harm when administered to a pregnant woman. Fulvestrant caused fetal loss or abnormalities in animals when administered during the period of organogenesis at doses significantly smaller than the maximum recommended human dose based on the body surface area. There are no adequate and well-controlled studies in pregnant women using fulvestrant.

GSK525762: As described in the GSK525762 IB Section 4.4.4 [GlaxoSmithKline Document Number 2011N113741_07], female fertility was affected in rats given 30 mg/kg/day GSK525762 for 15 days prior to mating and 15 days prior to mating through to Day 6 post coitus (pc). No fertility effects were observed when 30 mg/kg/day was given for 6 weeks followed by 6 weeks off-dose prior to mating. Reproductive and developmental toxicity occurred in rats given GSK525762 ≥1mg/kg/day from conception through gestation day 17 (of 21 days) and when dosed at ≥10 mg/kg/day for 14 days and dosing stopped prior to mating or continued until Day 6 pc.

In the BET115521 and BET116183 clinical trials, no pregnancies have been reported and all females of childbearing potential have been required to use non-hormonal forms of birth control with a failure rate of less than one percent. Similarly, there have been no reports of pregnancy resulting from males on study with female partners of childbearing potential. Refer to the GSK525762 IB for full details.

Monitoring and Management: Based on the findings in these reproductive and developmental toxicity studies in animals with both fulvestrant and GSK525762, there is a substantiated risk for adverse effects on embryo-fetal development and impacts on female fertility. Consequently, the proposed study will include strict contraceptive requirements for females of child-bearing potential (Section 6.10.2), described in Appendix 4. Pregnancy tests will be required at screening and periodically during the study for all women of child-bearing potential, as indicated in the Time and Events table (Section 7.1). Women who become pregnant while on study will be required to discontinue therapy and will be followed as described in Appendix 4.

4.7.1.1.5. General Toxicity Findings

Fulvestrant: As described in the fulvestrant package insert (Section 12.2), fulvestrant was associated with fatigue in 8% of subjects receiving the approved dose of 500 mg IM.

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

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

4.7.1.2. Predicted Single-Agent Toxicities

4.7.1.2.1. Cardiovascular Safety Findings

Fulvestrant: No significant cardiovascular safety findings have been described.

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

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

Monitoring and Management: Subjects will be monitored closely for changes in QTc with 12-lead ECG and for elevations in plasma troponin. Safety ECGs will be performed at the time points specified in Time and Events tables (Section 7.1) using a standard 12-lead ECG machine that automatically calculates the heart rate (HR) and measures PR, QRS, QT and QTcF intervals. As clinically indicated, the mean from triplicate ECGs will be evaluated. Safety ECGs will be reviewed by the investigator on an ongoing basis for safety purposes. Dosing should not begin until the safety ECG has been reviewed and no significant abnormalities have been detected.

To monitor for cardiomyopathy, echocardiograms or multigated acquisition (MUGA) scan will be performed at the time points specified in the Time and Events tables (Section 7.1). Management guidelines (Appendix 2) and stopping criteria (Section 5.4.2 and Section 5.4.3) are incorporated in the protocol. Please refer to the study reference manual (SRM) for further detail.

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

4.7.2. Benefit Assessment

Study 201973 is a Phase I/II dose-escalation and expansion study, and the first study of a BET inhibitor with the ER-degrading agent fulvestrant in women with metastatic or advanced ER+BC who have progressed on at least one line of prior endocrine therapy.

Both GSK525762 and fulvestrant have been administered as single agents to women with HR+BC, and fulvestrant is currently approved as a single agent and in combination with other agents to treat ER+BC. Data obtained in study 201973 may provide a novel mechanism to overcome resistance in subjects with advanced or metastatic ER+BC. In addition, this study will advance the molecular understanding of advanced malignancies and their treatment, and potentially help identify individuals more likely to benefit or have side effects from GSK525762 and/or fulvestrant.

4.7.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimise the risk to subjects participating in Phase I/II clinical trials, and potentially enriching for HR+/HER2- BC subjects who may respond to the combination of a BET inhibitor and an estrogen receptor antagonist, the potential risks identified in association with GSK525762 and fulvestrant are justified by the anticipated benefits that may be afforded to subjects with advanced or metastatic HR+/HER2- BC, who have failed prior therapies.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

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

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

5.1. Inclusion Criteria

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

1. Written informed consent provided
2. Females 18 years old and greater (at the time of written consent)
3. Histologically or cytologically confirmed diagnosis of advanced or metastatic adenocarcinoma of the breast.
4. Documentation of ER-positive and/or PR-positive tumor (≥1% positive stained tumor cell nuclei) based on local testing of the most recent tumor biopsy, using an assay consistent with local standards.
5. Documentation of HER2-negative tumor based on local testing of the most recent tumor biopsy, as per most recent American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines [Wolff, 2013]. At the time of writing, HER2-negative tumor is defined as immunohistochemistry (IHC) score of 0 or 1+, or negative by *in situ* hybridization defined as a HER2/CEP17 ratio <2 or for single probe assessment of an average HER2 copy number <4.
6. Provision of mandatory screening fresh tumor biopsy sample during the screening period.
    a. Screening biopsy can be waived if a biopsy was collected within 3 months prior to first dose of study drug and was collected after the last anti-cancer treatment before coming into this study.
    b. Subjects with inaccessible site of biopsy or who have a significant medical risk of obtaining the biopsy should be discussed with the Medical Monitor if they can qualify.
    c. Bone biopsies are not acceptable. Biopsies should be obtained from bone with metastatic soft-tissue component. Subjects with bone only disease may be enrolled upon review by Medical Monitor.
7. History of prior therapy that satisfies one of the following criteria:
    a. AI failures: Disease that relapsed during treatment or within 12 months of completion of adjuvant therapy with an AI, OR disease that progressed during treatment with an AI for advanced/metastatic disease. Prior ovarian suppression and/or tamoxifen are allowed as long as other criteria are met.
    b. CDK4/6 inhibitor plus AI failures: Disease that progressed on a CDK4/6 inhibitor plus AI, for advanced/metastatic disease with a minimum duration of treatment of 12 months (≥12 mo) with CDK4/6 inhibitor plus AI. Subjects with either measurable disease or bone only disease are allowed. Prior ovarian suppression and/or tamoxifen are allowed as long as other criteria are met.
8. Documented progression on last line of systemic anti-cancer therapy with CDK4/6 inhibitor + AI is required.
9. Any menopausal status

    NOTE: If pre- or peri-menopausal at time of enrollment (refer to Section 6.10.2.1 for menopause definition), subject must be willing to initiate therapy or continue ongoing therapy with goserelin for at least 28 days prior to the first dose of fulvestrant.

Subjects on an alternative Luteinizing hormone-releasing hormone (LHRH) agent do not have to start goserelin prior to the first dose of fulvestrant, but they must agree to change to goserelin at the next scheduled dose and remain on goserelin for the remainder of the trial

10. Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria is required except for subjects with bone only disease.
11. All prior treatment- related toxicities must be NCI-CTCAE v4 ≤ Grade 1 (except alopecia (permitted at any grade) and peripheral neuropathy (permitted at ≤ Grade 2) at the time of treatment allocation.
12. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 to 1 (See Appendix 5 for definitions).
13. Adequate organ function as defined in Table 2.

Table 2 Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥1.5 X 10^9/L
Hemoglobin	≥9 g/dL (subjects that required transfusion or growth factor need to demonstrate stable hemoglobin for 7 days of 9 g/dL)
Platelets	≥100 X 10^9/L
PT/INR and PTT	≤1.5 X upper limit of normal (ULN)
Hepatic	
Albumin	≥2.5 g/dL
Total bilirubin	≤1.5 x ULN[a]
ALT	≤2.5 × ULN OR <5 x ULN is acceptable for subjects with documented liver metastases/tumor infiltration
Renal	
Creatinine OR Creatinine clearance [either directly measured or calculated by Cockcroft-Gault formula[b]	≤1.5 X ULN ≥ 50 mL/min
Cardiac	
Ejection fraction	≥ LLN by echocardiogram or MUGA scan
Troponin (I or T)	≤ ULN

a. Isolated bilirubin >1.5 X ULN is acceptable if bilirubin is fractionated and direct bilirubin <35% or subject has a diagnosis of Gilbert's syndrome
b. Refer to Appendix 6 for Cockcroft-Gault formula

14. Able to swallow and retain orally administered medication.
15. A female subject is eligible to participate if she is of:

- Non-childbearing potential defined in Section 6.10.2.1
- Child-bearing potential as defined in Section 6.10.2.2, and agrees to use one of the contraception methods as described in Appendix 4.

- Negative serum pregnancy test ≤7 days prior to first study drug dose.
- Female subjects who are lactating must discontinue nursing prior to the first dose of study treatment and must refrain from nursing throughout the treatment period and for at least 28 days following the last dose of study treatment.

5.2. Exclusion Criteria

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

1. Prior therapy with any BET inhibitor, any selective estrogen receptor degrader (SERD) including fulvestrant, or inhibitors of the PI3K/AKT/mTOR pathway.
2. Prior therapy with more than one line of cytotoxic chemotherapy following diagnosis of advanced/metastatic disease.
3. ≥3 lines of systemic anti-cancer therapy in the advanced or metastatic setting.

   NOTE:

   a. Prior systemic anti-cancer therapy (cytotoxic chemotherapy, hormonal, CD4/6K inhibitor therapies) in the neoadjuvant/adjuvant setting does not count toward the lines of therapy.

4. Recent prior therapy, defined as:

   a. Any investigational or approved non-biologic anti-cancer drug within 14 days or five half-life (whichever is greater) prior to the first dose of GSK525762 and fulvestrant.
   b. Any nitrosoureas or mitomycin C within 42 days prior to the first dose of GSK525762 and fulvestrant
   c. Any anti-cancer biologic agents within 42 days prior to the first dose of GSK525762 and fulvestrant
   d. Any radiotherapy within 14 days prior to the first dose of GSK525762 and fulvestrant. If the subject received radiotherapy <90 days prior to study treatment, the irradiated lesion cannot be the only lesion used for evaluating response.
   e. Any major surgery within 28 days prior to the first dose of GSK525762 and fulvestrant

5. Concomitant active malignancy other than HR+/HER2- BC

NOTE: Subjects who have been disease-free and off therapy for 2 years, or subjects with a history of treated early stage cancers such as completely resected non-melanoma skin cancer or successfully treated *in situ* carcinoma of the cervix are eligible. Subjects with second malignancies that are indolent or definitively treated may be enrolled even if less than 2 years have elapsed since treatment. Consult Medical Monitor if unsure whether second malignancies meet requirements specified above

6. Therapeutic-dose anticoagulation (e.g., warfarin, low-molecular weight heparin [LMWH], or novel oral anticoagulants) must be discontinued and coagulation parameters must be normalized prior to the first dose of GSK525762 and fulvestrant.

Prophylactic anticoagulation, with low doses (per standard practice) of agents such as low molecular weight heparin (LMWH), direct thrombin inhibitors, or factor Xa inhibitors is permitted.

7. Current use of a prohibited medication or planned use of any forbidden medications during treatment with GSK525762 and fulvestrant. This includes medications with significant risk of Torsades de pointes as well as those that are potent inducers or inhibitors of CYP3A4 enzymes (see Section 6.11.2.1 for the list of prohibited medications).
8. Evidence of severe or uncontrolled systemic diseases (e.g., unstable or uncompensated respiratory, hepatic, renal, cardiac disease, or clinically significant bleeding episodes). Any serious and/or unstable pre-existing medical (aside from malignancy), psychiatric disorder, or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures, in the opinion of the Investigator.
    a. Systolic blood pressure higher than 150 mmHg or diastolic blood pressure higher than 90 mmHg found on 2 separate occasions separated by 1 week, despite adequate therapy, will be defined as uncontrolled hypertension.
    b. Uncontrolled diabetes mellitus (despite therapeutic; compliance to intervention) as defined by a haemoglobin A1c (HbA1c) level more than 8% and/or occurrence of more than two episodes of ketoacidosis in the 12 months prior to the first dose of study drug.
9. Subjects with advanced/metastatic, symptomatic, visceral spread, that are at risk of life-threatening complications in the short-term including subjects with massive uncontrolled effusions (pleural, pericardial, peritoneal), pulmonary lymphangitis, and over 50% of liver involvement in metastases.
10. Symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression.

    NOTE: Subjects previously treated for Central nervous system (CNS) metastases that have had stable CNS disease (verified with consecutive imaging studies) for at least 1 month, are asymptomatic and off corticosteroids, or are on stable dose of corticosteroids for at least 4 weeks prior to study Day 1 are permitted. Subjects currently taking enzyme-inducing anticonvulsant (EIAC) must be transitioned to non-enzyme inducing anticonvulsants prior to enrollment.
11. Cardiac abnormalities as evidenced by any of the following:
    - Baseline QTcF interval ≥480 msec
    - Clinically significant conduction abnormalities or arrhythmias
    - **NOTE**: Any clinically significant ECG assessments should be reviewed by the site cardiologist prior to study entry.
    - Presence of cardiac pacemaker or defibrillator with a paced ventricular rhythm limiting ECG analysis.
    - History or evidence of current ≥Class II congestive heart failure as defined by New York Heart Association (NYHA).

- History of acute coronary syndromes (including unstable angina and myocardial infarction), coronary angioplasty, or stenting within the past 3 months. Subjects with a history of stent placement requiring ongoing antithrombotic therapy (e.g., clopidogrel, prasugrel) will not be permitted to enroll.
- Clinically significant cardiomegaly, ventricular hypertrophy, or cardiomyopathy

12. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases or otherwise stable chronic liver disease per investigator assessment).
13. Presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening.

    NOTE: Subjects with positive Hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative Hepatitis C RNA PCR is obtained.
14. History of known HIV infection.
15. Any serious known immediate or delayed hypersensitivity reaction(s) to GSK525762 or fulvestrant, or idiosyncrasy to drugs chemically related to the investigational drugs.
16. Hemoptysis >1 teaspoon in 24 hours within the last 28 days.
17. Concurrent use of NSAIDs (except for cases where NSAIDs provide benefit over other analgesics and in these cases, consideration should be given to the prophylactic administration of a proton pump inhibitor) and high dose aspirin (allowed up to ≤100 mg PO daily). Details are available in 6.11.2.1.
18. Subjects with history of known bleeding disorder(s) including clinically significant hemorrhage (e.g., GI, neurologic), within the past 6 months.
19. Any clinically significant gastrointestinal (GI) abnormalities that may alter absorption, such as malabsorption syndrome, chronic gastrointestinal disease, or major resection of the stomach and/or bowels that could preclude adequate absorption of the study medication.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, and meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Appendix 10).

5.4. Withdrawal/Stopping Criteria

Subjects will receive study treatment until disease progression, death or unacceptable adverse event, including meeting stopping criteria for liver chemistry, hematologic/non-hematologic toxicity, QTc prolongation, or left ventricular ejection fraction (LVEF)/valvular dysfunction as defined in Section 5.4.1 through Section 5.4.4. Subjects may be permitted to continue on therapy in the setting of equivocal progression (e.g., rising tumor markers early in therapy in the absence of confirmed radiographic

progression, or equivocal radiographic imaging as described in Appendix 7) provided that the subject is not experiencing significant toxicity, the investigator believes (and the Medical Monitor concurs) that the subject may continue to receive benefit, and the subject has no other reasonable option for therapy that will provide long-term control of disease.

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

- deviation(s) from the protocol
- request of the subject or proxy (withdrawal of consent by subject or proxy)
- investigator's discretion
- subject is lost to follow-up
- study is closed or terminated
- a dose delay of >14 days unless the investigator and Medical Monitor agree that further treatment may benefit the subject
- pregnancy
- discontinuation from combination treatment, or of GSK525762 with continuation on fulvestrant monotherapy for >6 months

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. All subjects who discontinue from study treatment will have safety assessments at the time of discontinuation and during post-study treatment follow-up as specified in Section 7.1.

If a subject withdraws consent from the study, no further assessments will be completed, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

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

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

The primary reason study treatment was permanently discontinued must be documented in the subject's medical records and electronic CRF.

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

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

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

In Phase II, individual prior treatment history-specific cohorts may be terminated if they meet criteria for toxicity or lack of efficacy as described in Section 9.1.2. Any subject already enrolled in a terminated cohort may continue to receive therapy per protocol.

In Phase II, unless a disease cohort is closed early, survival follow-up will continue in each cohort until approximately 70% of the total number of subjects have died. At such time, the study will be considered completed and any further follow-up on subjects enrolled will cease.

Subjects who require permanent discontinuation of one of the study treatments in a given combination may continue on the other treatment until disease progression, withdrawal of consent, or unacceptable toxicity after discussion with Medical Monitor. With the implementation of amendment 06, subjects who have permanently discontinued treatment with the combination, or of GSK525762 but have remained on fulvestrant monotherapy for >6 months should be discontinued from study.

At the time of study completion, subjects with radiologically confirmed lack of disease progression (from Phase I and Phase II) who are still receiving GSK525762 and/or fulvestrant may continue treatment through a separate mechanism (e.g., roll-over protocol) to be determined at that time.

Enrolment into the study is now closed. The study will conclude when the last subject has completed/discontinued study treatment and completed the end of treatment visit.

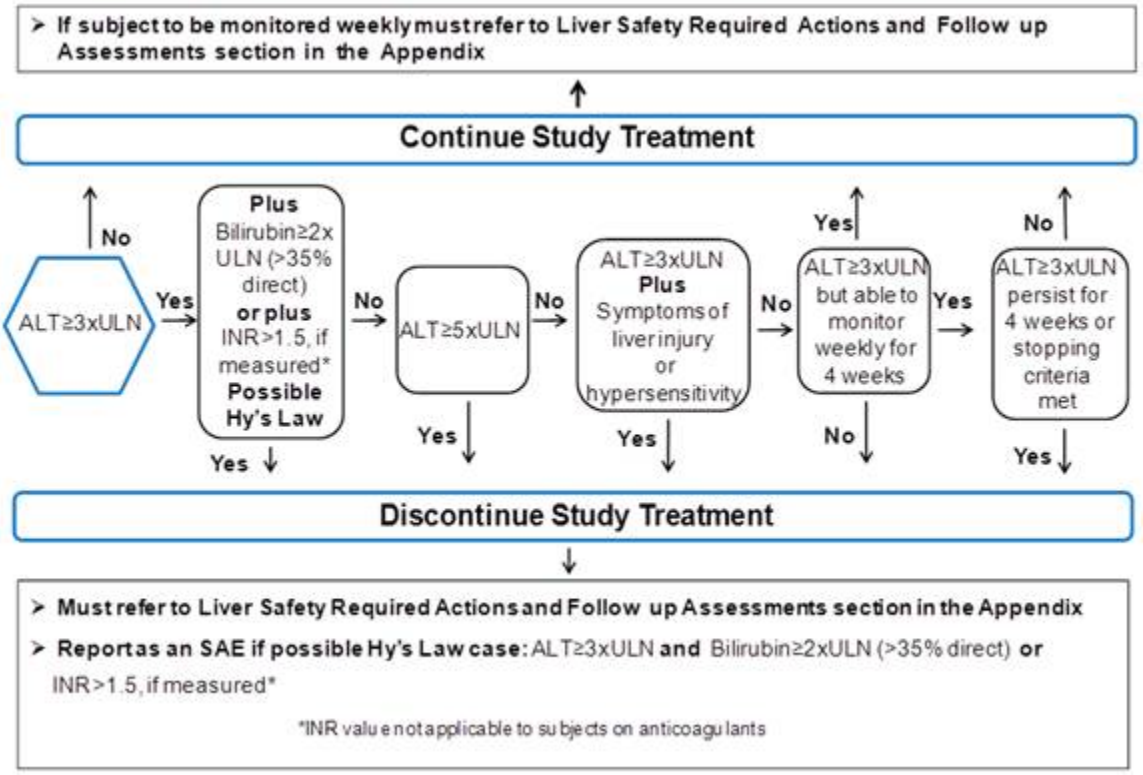
5.4.1. Liver Chemistry Stopping Criteria

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

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

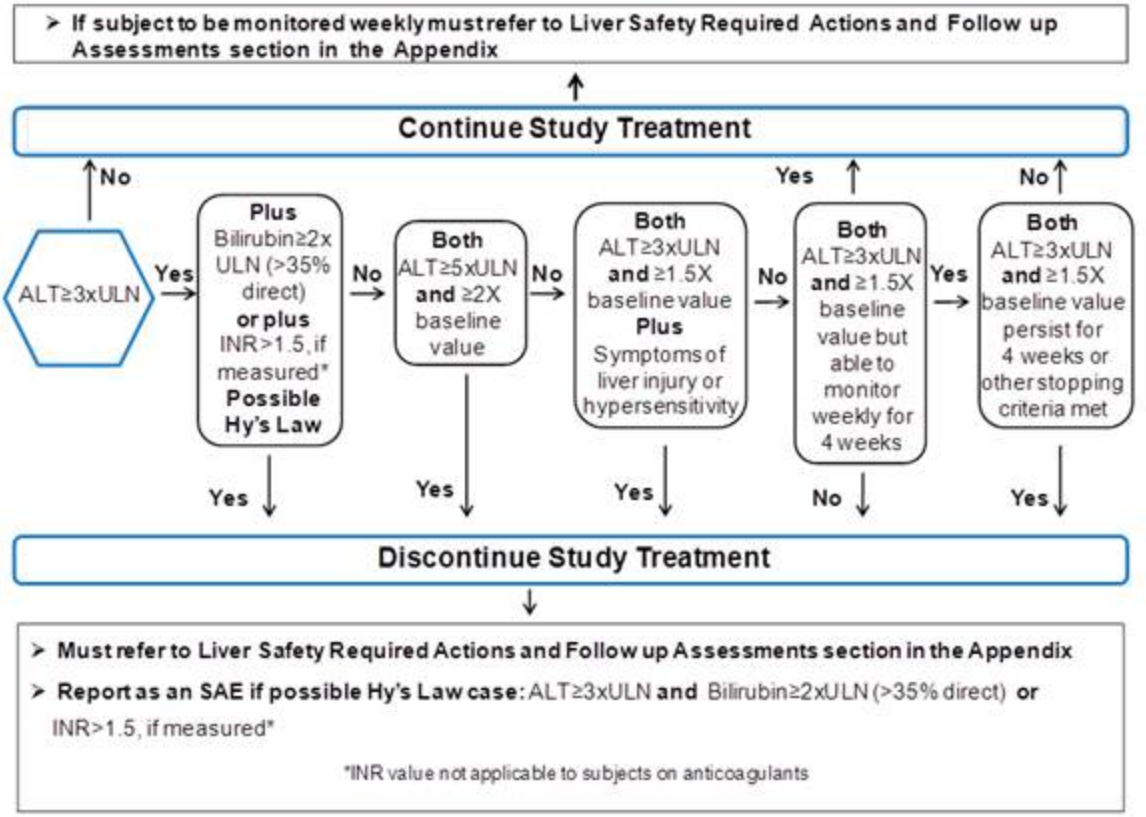
See Figure 4 and Figure 5 for liver stopping criteria for subjects without and with liver metastases, respectively. The algorithms are best read from left to right.

Figure 4 Phase I/II Liver Chemistry Stopping and Increased Monitoring Algorithm for Subjects WITH entry criteria ALT ≤2.5xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 8.

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



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 8.

5.4.1.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any subject participating in this study is not allowed.

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

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

Refer to Appendix 9 for full guidance.

5.4.2. QTc Stopping Criteria

For the purposes of this study, the corrected QT (QTc) is the QT interval corrected for heart rate according to Fridericia's formula (QTcF; defined as $[QT/(RR^{1/3})]$). QTcF will

be used for all subjects for purposes of eligibility, data analysis, and withdrawal. The QTcF should be based on averaged QTcF values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

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

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

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

5.4.3. Left Ventricular Ejection Fraction (LVEF) Stopping Criteria

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

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

5.4.4. Other Stopping Criteria

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

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

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

5.5. Subject and Study Completion

In Phase I and II, a subject will be considered to have completed the study if they are followed until death.

Subjects who have not died and are no longer being followed for survival are considered to have discontinued the study. The End of Study electronic Case Record Form (eCRF) should only be completed when a subject is no longer being followed. The study will be considered completed for purposes of final analysis when approximately 70% of the subjects enrolled in Phase II have died. However, the study could be stopped due to toxicity or futility before that when there is enough evidence to conclude as such.

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. Enrolment into the study is now closed.

With the implementation of Amendment 06, specific assessments and collection of survival follow-up data will no longer be required. Please see Section 7.1 for further details. The study will conclude when the last subject has completed/discontinued study treatment and completed the end of treatment visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

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

Investigational Product (Phase 1)				
Product name:	GSK525762C Tablets			Fulvestrant
Unit dose strength(s)/Dosage level(s):	5mg	20mg	25mg	250 mg
Dosage form	Tablet	Tablet	Tablet	IM Injection
Manufacturer	GSK	GSK	GSK	AstraZeneca
Physical description:	White to slightly colored, round, biconvex tablet.			5-mL prefilled syringe containing 250 mg/5 mL fulvestrant. The solution for injection is a clear, colorless to yellow, viscous liquid.
Route/ Administration/ Duration:	**Oral;** see Time and Event Tables for schedule and administration timings			**IM**
Dosing instructions:	Dose with 240 mL liquid* and should be taken around the same time every day without regards to timing of meal (If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.)			Administer 500 mg intramuscularly into the buttocks slowly (1-2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29, and once monthly thereafter. There is a ±3-day dosing window for the fulvestrant.

NOTE: The Phase 1 formulation details are current at the time of protocol finalization and may be updated in other documents (e.g., SRM and/or informed consent form) without requiring protocol amendment. Phase 2 formulation details will be provided in an amendment.
*Subjects may take BET with 240 mL of liquid (other than orange, grapefruit, pomelo, or exotic citrus fruit juice). On serial PK days (W1D1 and W3D1), subjects must take BET with water only.

6.2. Treatment Assignment

6.2.1. Phase I

Subjects will be assigned to receive GSK525762 and fulvestrant in an open-label fashion. Placebo will not be administered in Phase I. Subjects will be identified by a unique subject number that will remain consistent for the duration of the study.

During the initial evaluation of DL1, subjects will be enrolled into their prior therapy-specific cohort. Data from the first 3-10 subjects (irrespective of cohort) will be used to determine if DL1 exceeds the MTD.

Once DL1 has been cleared in dose escalation, subjects will be enrolled into their prior therapy-specific cohort at DL2. Data from the first 3-10 subjects (irrespective of cohort) will be used to determine if DL2 exceeds the MTD. Any additional subjects (prior to

DL2 clearing) will be enrolled in one of two prior treatment history-specific cohorts at DL1.

Once DL2 has been cleared in dose escalation, enrolment will be prioritized to DL2 until it enrols the same number of subjects as DL1. After that subjects will be enrolled into the prior treatment-specific cohorts at either DL1 or DL2 provided that:

- There are remaining slots in the cohort
- Either cohort has not closed due to unacceptable toxicity or lack of efficacy

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

6.2.2. Phase II

With implementation of amendment 06, Phase II of the study is terminated.

Subjects who have disease that has progressed after prior treatment with either AIs or CDK4/6 inhibitor plus AI will be randomized 1:1 to receive either fulvestrant plus GSK525762 or fulvestrant plus GSK525762-matched placebo. Subjects will be assigned to their cohort in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

6.3. Planned Dose Adjustments

There are no pre-planned dose adjustments per protocol.

Subjects who experience toxicity may require dose delay and/or reduction of dose; for dose adjustment recommendations in response to toxicity, please refer to Appendix 2. Table 3 clarifies the dose reductions for GSK525762 at any planned dose level.

As described in Section 4.2.3.8, subjects receiving a dose below the RP2D at the end of Phase I may be dose escalated to a dose not to exceed the RP2D upon completion of Phase I.

Table 3 GSK525762 Dose Reductions

Current GSK525762 Dose:	If subject requires dose level reduction:
40 mg (DL-1)	No further dose reduction allowed
60 mg (DL1)	40 mg
80 mg (DL2)	60 mg

During any dose interruptions of GSK525762, fulvestrant may be continued at the protocol dose unless dose interruption of both products is required.

6.4. Blinding

Phase I of the study will be open-label. No blinding will be performed. Investigators will have direct access to the subject's individual study treatment.

Phase II of the study will double-blind. Based on results from Phase I, Phase II will enrol subjects who have disease that has progressed after prior therapy with:

- AIs alone (either in the setting of primary metastatic disease or on-treatment/within 12 months of discontinuing adjuvant endocrine therapy), OR
- CDK4/6 inhibitor plus AI, OR
- either AI therapy OR CDK4/6 inhibitor plus AI. If both cohorts are permitted to enroll in Phase II, randomization will be stratified by prior CDK4/6 inhibitor-based therapy (i.e., CDK4/6 inhibitor-naïve versus CDK4/6 inhibitor-exposed) and corresponding stratified analysis will be provided at interim and final analyses

In Phase II, eligible subjects will be randomized 1:1 to receive GSK525762 plus fulvestrant (Arm A), or fulvestrant plus GSK525762-matched placebo (Arm B), in a double-blinded fashion.

The following guidelines will apply to Phase II:

- The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator. In this case, the treatment allocation shall only be shared if necessary, and if feasible, with personnel involved in the clinical management of the subject. Personnel exclusively involved in the clinical trial conduct, e.g., study coordinators, study nurses, and representatives from Contract Research Organization (CRO)/GSK, shall remain blinded to the treatment allocation.
- **It is preferred (but not required)** that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.
- The date and reason for the unblinding must be fully documented in the CRF

A subject may continue in the study if that subject's treatment assignment is unblinded. If a subject is discontinued, the primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.5. Packaging and Labeling

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

6.6. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

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

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

6.7. Compliance with Study Treatment Administration

At study treatment dispensing visits, an evaluation of subject compliance with taken medication will be performed by reviewing the subject diary and reconciliation of tablet count for GSK525762. However, on W3D1 in both Phase I and Phase II, only review of the subject diary will occur. The investigator will make every effort to bring non-compliant subjects into compliance.

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

Compliance of study treatment administration will be assessed through querying the subject during the site visits and documented in the source documents and CRF.

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

6.8. Treatment of Study Treatment Overdose

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

GSK does not recommend specific treatment for an overdose.

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

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

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

6.9. Treatment after the End of the Study

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

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

6.10. Dietary and Lifestyle Restrictions

6.10.1. Dietary Restrictions

GSK525762 can be taken under fasting or fed conditions, except on serial PK sampling days (Week [W] 1 Day [D] 1 and W3D1) in Phase I, as described below.

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

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

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

6.10.2. Female Subjects

6.10.2.1. Menopause Definition & Female Subjects of Non-Childbearing Potential

For the purpose of this study (including eligibility), post-menopausal is defined as a subject who satisfies at least one of the following:

- Age ≥60 years old
- Age under 60 years old with 12 months of spontaneous amenorrhea (in the absence of alternative physiological, pharmacological, or pathological cause), and serum estradiol and follicule stimulating hormone (FSH) level within the local laboratory's reference range for postmenopausal females
- Medically confirmed ovarian failure
- Documented bilateral oophorectomy

Pre- and peri-menopausal women may be considered to be of non-childbearing potential provided they have undergone a documented hysterectomy, bilateral tubal ligation, or bilateral tubal occlusion procedure. Note, however, that these subjects must still be administered goserelin as described in Section 5.1.

6.10.2.2. Female Subjects of Childbearing Potential

Female subjects of childbearing potential must not become pregnant and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of ≤1% [Hatcher, 2011]. LHRH agonists/antagonists alone are insufficient for contraception for this study. Please refer to Section 12.4.1 for a full list of permitted methods of contraception.

6.11. Concomitant Medications and Non-Drug Therapies

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

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

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

6.11.1. Permitted Medications and Non-Drug Therapies

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, granulocyte colony-stimulating factors (GCSF) and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate. The only caveat is that subjects should not receive those medications listed as prohibited in Section 6.11.2.

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

6.11.2. Prohibited and Cautionary Medications and Non-Drug Therapies

6.11.2.1. Prohibited Medications

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

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

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

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

6.11.2.2. Prohibited Non-Drug Therapies

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

> **NOTE**: Subjects may receive focal palliative (e.g., for management of pain or other local symptom) radiation treatment and/or surgical intervention during this study.

Target lesions used for response assessment may not receive focal palliative therapy. Any proposed focal therapy must be approved by the investigator and the Medical Monitor prior to intervention.

Subjects will abstain from using herbal prescription/non-prescription preparations/medications throughout the study until the final study visit due to the limited data on potential CYP-mediated interactions produced by those products. Herbal products include, but are not limited to: St. John's Wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, ginseng, and marijuana.

6.11.2.3. Cautionary Medications

Subjects should minimize the use of medications that contain acetaminophen. If a subject requires medication for hyperemesis, due to the potential of serotonin 5-HT3 receptor antagonists to increase QT duration corrected for heart rate by Fridericia's formula (QTcF), palonosetron (administered per the prescribing information) and ondansetron (up to a maximum dose of 8 mg three times daily [TID]) are the only allowed drugs in this class. Intravenous administration is not allowed. Drugs with a low risk of causing QTc prolongation (e.g., aprepitant) may be used without restriction.

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

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

GSK525762 is a substrate for BCRP and Pgp transporters. Therefore, potent inhibitors of these transporters, such as cyclosporine, tacrolimus, or ketoconazole, should be used with caution, and additional monitoring for adverse effects should be utilized.

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

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

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

7. STUDY ASSESSMENTS AND PROCEDURES

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

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

The following points must be noted:

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

  Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.
- The timing and number of planned study assessments, may be altered during the course of the study based on newly available data to ensure appropriate monitoring. With the implementation of Amendment 06, specific assessments and collection of survival follow-up data will no longer be required. Please see Section 7.1 for further details.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment. All such changes will be incorporated in the protocol at the next earliest amendment.
- The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

7.1. Time and Events Table

Table 4 Time and Events, Phase I

Procedure	SCR	Week 1		Week 2		Week 3		Week 4	Week 5	q4w	q8w	q8w	q12w	EOT[1]
		D1	D4	D1	D4	D1	D4	D1	D1	W9 to W49	W9 to W49	W49 and thereafter	W49 and thereafter	
Screening[2]														
Informed Consent	X													
Demography	X													
Medical History	X													
Inclusion/Exclusion Criteria	X													
Disease Characteristics	X													
Prior Therapy[3]	X													
Register Subject	X													
Safety														
Physical Exam[4]	X	X		X		X		X	X	X			X	X
ECOG PS[5]	X	X		X		X		X	X	X			X	X
12-lead ECGs[6]	X	X	X	X		X		X	X	X			X	X
Clinical Laboratory Assessments[7]	X	X	X	X	X	X	X	X	X	X				X
Echocardiogram or MUGA[8]	X								X	Week 13, 25, 37, 49			X	X
PRO-CTCAE[9]	X													
Study Treatment														
Administer GSK525762[10]		Daily												
Administer Fulvestrant[10]		X				X			X	X				
AE/SAE review		Continuous from signing of informed consent												
Concomitant medication review		Continuous from signing of informed consent												

Procedure	SCR	Week 1		Week 2		Week 3		Week 4	Week 5	q4w	q8w	q8w	q12w	EOT[1]
		D1	D4	D1	D4	D1	D4	D1	D1	W9 to W49	W9 to W49	W49 and thereafter	W49 and thereafter	
Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)														
PK blood samples[11]														
Tumor biopsy[12]	X													
Whole blood for exploratory analyses[13]	X													
PGx blood sample[14]		X												
Efficacy														
CT chest/abdomen/pelvis[15]	X													
EORTC-QLQ-C30 & EORTC-QLQ-BR23[16]	X													

1. Applies to subjects who withdraw for any reason prior to progression or who progress during study treatment. **With the implementation of amendment 06, following the EOT visit, subjects will be no longer be contacted approximately every 3 months (± 14 days) to collect survival data.**
2. Screening procedures should be performed as rapidly as possible within 28 days prior to Day 1 (first dose of study medication) to facilitate subject entry requirements. Clinical lab assessments should be completed within 14 days prior to dosing, and in case of abnormal test values, retesting may be performed if medically indicated and within 14 days prior to Day 1. Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging studies, etc.) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within 28 days prior to Day 1 (first dose of study medication) unless otherwise indicated: CT scans (within 30 days prior to Day 1) and ECHO/MUGA (within 35 days prior to Day 1).
3. Including dates of imaging and sizes of target lesion(s) used for RECIST 1.1 evaluation, if available.
4. Complete physical examination required at screening, Week (W)1 Day (D)1 (W1D1), and end of the treatment (EOT) visits. Limited examinations permitted at all other visits, as noted. Definition of complete and limited examinations may be found in Section 7.3.1. Post Week 49, assessments will be completed every 12 weeks.
5. Post Week 49, ECOG assessments will be completed every 12 weeks.
6. Triplicate ECGs should be performed at screening. All other timepoints can be single ECGs prior to dosing and evaluated for abnormality prior to administration of dose. Post Week 49, assessments will be completed every 12 weeks. Triplicate ECGs to be performed as clinically indicated, based upon abnormal findings.
7. Refer to Table 5 for details of clinical safety labs and timing of collection
8. Whatever scanning modality is used at screening should be maintained for all subsequent scans. An assessment is not performed at W9. Beginning at W13, scans will be performed once every 12 weeks.
9. **With the implementation of amendment 06, the PRO-CTCAE will no longer be collected.**
10. Drugs should be administered as described in Section 6.1. Visits where fulvestrant is administered will be considered drug dispensing days. There is a ±3 day window for fulvestrant dosing. On PK collection days in Week 1 and Week 3, subjects should abstain from food from 8 h prior until 2 h after dose as described in Section 6.10.1. Post Week 49, fulvestrant will continue to be administered every 4 weeks. Refer to the SRM for further details.
11. **With the implementation of amendment 06, PK samples will no longer be collected.**
12. **With the implementation of amendment 06, tumor biopsies will no longer be collected, and the EOT tumor biopsy will no longer be collected.**

13. **With the implementation of amendment 06, whole blood for exploratory analyses will no longer be collected.**
14. **With the implementation of amendment 06, if a PGx sample has not yet been collected, collection will no longer be required.**
15. **With the implementation of amendment 06, contrast-enhanced computed tomography (CT) scan data will no longer be required for disease assessment.**
16. **With the implementation of amendment 06, EORTC questionnaires will no longer be collected.**

Table 5 Time and Events, Phase I Laboratory Assessments

	SCR [1]	Week 1		Week 2		Week 3		Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 11	q4w	q12w	EOT
		D 1	D 4	D 1	D 4	D1	D4	D1	D1	D1	D1	D1	D1	D1	W13 and after	W49 and after	
Clinical chemistry	X	X	X	X		X		X	X		X		X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X
Liver chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Troponin, N-terminal pro–B-Type natriuretic peptide (NT- proBNP)	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X
Coagulation	X	X	X	X		X		X	X		X		X	X	X	X	X
Factor VII Assay[2]	X					X			X								
Fasting blood glucose	X	X	X	X		X		X	X		X		X	X	X	X	X
HbA1c	X								X		X		X	X	X	X	X
Fasting lipids	X								X		X		X	X	X	X	X
Thyroid (Thyroid stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4))[3]	X								X		X		X	X	X	X	X
Pancreatic	X	X		X		X		X	X		X		X	X	X	X	X
Urinalysis	X	X		X		X		X	X		X		X	X	X	X	X
HIV, Hepatitis B surface antigen (HBsAg), Hepatitis C Virus (HCV) Antibody	X																
FSH/Estradiol[4]	X																
Pregnancy test[5]	X	X				X			X		X		X	X	X		X

1. Although strongly preferred, lab results for HBA1c, fasting lipids, TSH/T3/T4, and pancreatic enzymes are not required prior to dosing.
2. Also perform if PT or INR are ≥1.5XULN, or in case of bleeding event
3. TSH testing is mandatory. T4 testing is only required if TSH is abnormal. T3 testing is required when clinically applicable (if both TSH and T4 are abnormal).
4. Only required at screening for pre- and peri-menopausal subjects
5. Serum pregnancy test within 7 days prior to first dose; urine or serum test thereafter

7.2. Screening and Critical Baseline Assessments

Screening procedures should be performed as rapidly as possible within 28 days prior to Day 1 (first dose of study medication) to facilitate subject entry requirements. Clinical lab assessments should be completed within 14 days prior to dosing, and in case of abnormal test values, retesting may be performed if medically indicated and within 14 days prior to Day 1.

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5. Medical, surgical, and treatment history including date of first diagnosis, best response to prior systemic therapy, histology, and current sites of disease will be taken as part of the medical history and disease status. Measurement(s) of target lesion(s) should be provided for at least two prior disease evaluations, if available. Details concerning concomitant medication will be recorded starting from screening through post-study follow-up. At a minimum, the drug name, route of administration, dose and frequency of dosing, along with start and stop dates should be recorded.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging studies, etc.) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed 28 days prior to Day 1 (first dose of study medication) unless otherwise indicated: CT scans (within 30 days prior to Day 1) and ECHO/MUGA (within 35 days prior to Day 1).

Investigators may be requested to perform additional safety tests during the course of the study based on newly available data to ensure appropriate safety monitoring. Appropriate local regulatory and ethical approvals should be obtained before any additional testing is performed.

7.2.1. Critical Baseline Assessments

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

- All subjects should have a contrast-enhanced (oral and IV) CT scan of the chest, abdomen, and pelvis performed. Baseline imaging should be completed within 30 days prior to the first dose of study drug. Baseline characterization of target- and non-target lesions should be performed as described in Appendix 7. For subjects with a contraindication to contrast-enhanced CT (e.g., documented allergy to iodinated contrast), then other modalities, such as non-enhanced CT of the chest and gadolinium-enhanced magnetic resonance imaging (MRI) of the abdomen and pelvis, may be used after discussion with the medical monitor. At each post-baseline assessment, re-evaluation of the site(s) of disease identified by these scans, using the same imaging modality, is required.

A baseline tumor biopsy sample is required for all subjects, as follows:

- Phase I:
  - All subjects must provide a biopsy sample at screening. A fresh biopsy specimen must be provided within 28 days prior to first study dose. A sample collected within 3 months of first dose is also acceptable only if it was collected after the last anticancer treatment.
  - Subjects with bone only disease without any visceral tumor tissue amenable to biopsy may be enrolled without a biopsy sample only upon review by medical monitor
  - Paired on treatment fresh biopsies are optional but encouraged. All subjects enrolled in the study will be asked to provide paired fresh biopsies pre- and post-dose at the time points indicated in Section 7.1, as described in Section 7.5.1. Fresh biopsies should be paired with plasma samples for PK, collected as close as possible to the biopsy (ideally within 1 h). Subjects should have at least four consecutive doses of GSK525762 prior to collection of tumor biopsy, whether they have had a dose interruption or not. Subjects will be informed at the time of informed consent whether paired fresh biopsies will be required. If a potential subject does not have a disease amenable to biopsy, participation may occur only upon discussion and approval of the medical monitor. Further details regarding sample type and processing will be provided in the SRM.
- Phase II:
  - All subjects must provide a fresh tissue specimen at screening. If an archival specimen is not available, then a fresh pre-treatment biopsy specimen must be provided. On-study biopsies are not required

7.2.2. Visit Windows

With the implementation of amendment 06, specific assessments and collection of survival follow-up data will no longer be required. Please see Section 7.1 for further details.

Screening (baseline to pre-dose): Screening echocardiogram or MUGA scan should be completed within 35 days prior to the first dose of study drugs. Baseline imaging should be completed within 30 days prior to the first dose of study drug. Clinical lab assessments should be completed within 14 days prior to first dose of study drugs. Clinical labs performed during screening within 72 hours of first dose do not need to be repeated on Day 1. All other assessments should be completed with 28 days prior to first dose of study drug.

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

Week 2: Based on subject and clinic schedule, assessments can be ± 3 days.

Week 3: Assessments on Week 3 Day 1 may be delayed up to 2 days. Assessments on Week 3 Day 4 may be scheduled ± 3 days.

Note: The Week 3 Day 1 PK collection is timed to permit evaluation of GSK525762 PK at steady-state dosing (at least 7 consecutive days dosing prior to collection). If a subject is not receiving GSK525762 on Week 3 Day 1 (due to toxicity), then serial PK collection should be rescheduled for a later timepoint when the subject is again being dosed for at least 7 consecutive days, and the alternate collection date noted in the eCRF. However, in this case a single pre-dose sample should still be collected to evaluate for fulvestrant trough concentration.

Weeks 4, 5, and 9: Clinic visits may be scheduled ± 3 days. The first disease assessment (at Week 9) may be scheduled ± 7 days.

Weeks 6, 7, 8, and 11: Lab visits may be scheduled ± 7 days.

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

Every 4-week, 8-week, and 12-week visits after Week 49: Every 4-week visits (and their associated laboratory studies) are no longer required, based on clinical judgment. Every 8-week and 12-week clinic visits can be scheduled ± 7 days.

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

7.3. Safety

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

7.3.1. Physical Exams

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

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

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

Vital signs should be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate.

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

Investigators should pay special attention to clinical signs related to previous serious illnesses, as well as to any prior toxicity or other event while on study. Any visible or palpable disease should be noted for response or progression as described in Appendix 7.

7.3.2. ECOG Performance Status

The performance status will be assessed using the ECOG scale (Appendix 5) as specified in Section 7.1.

7.3.3. Cardiac Safety

7.3.3.1. Electrocardiograms

Triplicate 12-lead ECGs will be obtained at screening. On treatment single ECGs will be completed, prior to dosing, on days specified in Section 7.1 during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Details will be provided in the SRM. Any values >480 msec as calculated by the machine must be confirmed manually according to Fridericia's formula. Refer to Section 5.4.2 for QTcF calculations and QTc withdrawal criteria, and to Appendix 2 for management strategies for QTcF prolongation. Triplicate ECGs should be performed as clinically indicated, due to abnormal findings.

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

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

ECG data may be transferred to a central facility for collection. Any central data may be reviewed by an independent central reviewer for retrospective analysis. With the implementation of amendment 06, transfer of ECG data to a central facility is no longer required.

7.3.3.2. Echocardiogram or Multigated Acquisition Scan

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

Scan data may be transferred and reviewed by an independent cardiologist. Instructions for submission of qualifying scans are provided in the SRM. With the implementation of amendment 06, transfer of scan data for independent cardiologist review is no longer required.

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

7.3.4. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 6, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events tables. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

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

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

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

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

Table 6 Clinical Laboratory Tests

Clinical Chemistry		
Sodium Potassium Chloride Total Carbon Dioxide Blood Urea Nitrogen* Creatinine	Fasting Glucose Magnesium Calcium (total and ionized) Total Protein Albumin	
Hematology		
White blood cell count Hemoglobin Platelet count	*Automated White Blood Cell Differential:* Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Liver Function		
Bilirubin (Total and Direct)** Aspartate Aminotransferase Alanine Aminotransferase Alkaline Phosphatase		
Routine Urinalysis		
Specific gravity, pH, glucose, protein, blood, and ketones by dipstick Microscopic examination (if urinalysis is abnormal, if available at participating site) Urine hCG pregnancy test (only for women of child bearing potential. Note that initial screening test must be serum hCG and subsequent tests may be serum or urine hCG)		
Cardiac Studies		
Troponin (I or T), may be collected at central laboratory if local draw is not possible NT-proBNP Fasting Lipid panel (Total Cholesterol, LDL, HDL, triglycerides)		
Other Studies		
Coagulation Studies: Prothrombin Time/INR Partial Thromboplastin Time or Activated Partial Thromboplastin Time (aPTT) Fibrinogen Factor VII Assay	**Endocrine Studies:** Thyroid-stimulating hormone (TSH) Free Thyroxine 3 (Free T3) Free Thyroxine 4 (Free T4) Hemoglobin A1c FSH and estradiol (for pre- and peri-menopausal subjects only)	**Safety Screening Studies:** HIV, HbSag, HCV antibody **Pancreatic Markers:** Amylase Lipase

*Direct and/or calculated BUN values are acceptable.
**Direct Bilirubin is only required if total bilirubin values are abnormal.
NT-ProBNP = N-terminal pro b-type natriuretic peptide; LDL = Low-density lipoprotein; HDL = High-density lipoprotein; INR = International normalized ratio; HIV = Human immunodeficiency virus; HBsAg = Hepatitis B surface antigen; HCV = Hepatitis C virus
Note: Not all studies are performed at each visit; please refer to Section 7.1, Table 5 for timing of required studies

7.3.5. Adverse Events (AEs) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 10. The severity of adverse events will be graded utilizing the NCI-CTCAE v4. Additional details regarding management of specific AEs or SAEs are described in Section 5.4, Appendix 2, and Appendix 10.

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

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

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

- AEs and SAEs will be collected from the signing of informed consent until the end of study visit (Section 7.3.5.3), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK or designee within 24 hours, as indicated in Appendix 10.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK or designee.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 10.

7.3.5.2. Method of Detecting AEs and SAEs

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

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

7.3.5.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs (as defined in Appendix 10) will be followed until resolution, until the condition stabilizes, until the

event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 10.

7.3.5.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 10 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

7.3.5.5. Other sentinel events

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

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

Any new primary cancer must be reported as a SAE.

7.3.5.6. Regulatory Reporting Requirements for SAEs

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

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

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

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

7.3.6. Pregnancy

Details of all pregnancies in female participants will be collected after the start of study treatment and until at least 90 days post-last dose.

If a pregnancy is reported then the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined Appendix 4.

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

7.4. Pharmacokinetics

With the implementation of amendment 06, PK samples will no longer be collected.

Blood samples for pharmacokinetic (PK) analysis of fulvestrant and GSK525762 (including relevant metabolite[s]) will be collected at the time points indicated in Table 4. While GSK525762 PK samples will be collected at all time points starting on Week 1 Day 1, only the pre-dose samples will be analyzed for fulvestrant. The actual date and time of each blood sample collection will be recorded. Subjects should be instructed to withhold their dose of orally administered study drugs, including GSK525762 and fulvestrant, until after the pre-dose pharmacokinetic blood sample is collected.

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

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

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

7.5. Pharmacodynamics

With the implementation of amendment 06, tumor samples will no longer be collected.

Tumor samples will be collected pre-dose and on-treatment from a limited number of subjects in order to evaluate for changes in molecular markers of BET inhibition (e.g., expression of proteins regulated by BET proteins) and HR signalling.

7.5.1. Tumor Biopsy Collection/Surgical Procedures

A mandatory fresh tumor biopsy sample is required for all subjects during the screening period within 28 days of the first dose of study treatment. A sample collected within 3 months of first dose is also acceptable only if it was collected after the last anti-cancer treatment. Bone biopsy sample is not acceptable. Biopsy requirement for subjects with bone only disease with no visceral tumor may be waived only upon review by GSK.

a. Screening biopsy can be waived if a biopsy was collected within 3 months prior to first dose of study drug and was collected after the last anti-cancer treatment before coming into this study.
b. Subjects with inaccessible site of biopsy or who have a significant medical risk of obtaining the biopsy should be discussed with the Medical Monitor if they can qualify.
c. Bone biopsies are not acceptable. Biopsies should be obtained from bone with metastatic soft-tissue component. Subjects with bone only disease may be enrolled upon review by Medical Monitor.

On treatment fresh biopsies are optional but encouraged. Subjects providing an on-treatment fresh tumor biopsy must have received at least 4 consecutive doses of GSK525762 prior to the collection of the tissue. A limited number of additional subjects may be requested to provide pre and on-treatment biopsies based on emerging data. Biopsy requirement(s) will be discussed with the subject prior to signing informed consent. Any fresh on-treatment biopsy should be accompanied by a plasma sample collected as close as possible to the time of biopsy (preferably within 1 h).

Subjects must have a platelet count of $\geq 75{,}000/mm^3$ and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy or any other planned surgical procedure. Further details regarding sample type and processing will be provided in the SRM.

7.6. Evaluation of Anti-Cancer Activity

With the implementation of amendment 06, CT scan data will no longer be required for disease assessment. See the Time and Events Table (Section 7.1) for the updated schedule of assessments.

Tumor response will be assessed as outlined in the Time and Event Tables by the investigator using RECIST 1.1 (Appendix 7) guidelines and documented in the eCRF as: progressive disease (PD), stable disease (SD), partial response (PR), and complete response (CR). See the SRM for additional instructions.

Lesion assessment method and timing, evaluation of disease, disease progression and response will be conducted according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [Eisenhauer, 2009] as outlined below and in Appendix 7 of this protocol. Disease assessment modalities may include imaging (CT scan, MRI, bone scan, plain radiography). Contrast-enhanced CT of the chest, abdomen, and pelvis at each disease

assessment timepoint is the preferred imaging modality. However, subjects with contraindication to CT may have other modalities performed as clinically indicated.

The baseline disease assessment will be completed within 30 days prior to the first dose of GSK525762 and fulvestrant, then approximately every 8 weeks thereafter and at the final study visit.

- Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays.
- For post-baseline assessments, a window of 5-7 days is permitted to allow for flexible scheduling (see Section 7.2.2). If the last radiographic assessment was more than 14 days prior to the subject's withdrawal from study and progressive disease has not been documented, a disease assessment should be obtained at the time of withdrawal from study.
- Subjects whose disease responds (either CR or PR) should have a confirmatory disease assessment performed no less than 4 weeks after the date of assessment during which the response was demonstrated. The next assessment following a confirmatory disease assessment should follow the regular schedule, occurring approximately 4 weeks after the confirmatory assessment.
- To ensure comparability between the baseline and subsequent assessments, the same method of assessment and the same technique will be used when assessing response.

7.6.1. Phase I

GSK requires sites to provide electronic copies (upload digital images or images on CD) of scans for all subjects for central storage which may be transferred to a central independent imaging center. This includes baseline scans and all scans performed during the course of the study. GSK may request an independent review of scans. See the SRM for additional details.

7.6.2. Phase II

GSK requires sites to provide electronic copies (upload digital images or images on CD) of scans for all subjects for central storage which will be transferred to a central independent imaging center. Evaluation of response and PFS will be made by the Investigator/site radiologist as well as by an independent reviewer who is blinded to the subject's therapy assignment. See the SRM for additional details.

7.7. Translational Research

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

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

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

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

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

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

7.7.1. Tumor Biomarker Analysis

To further characterize the subject population, DNA, RNA and/or protein measurements may be utilized to identify predictors of sensitivity or resistance to GSK525762 and fulvestrant in combination utilizing baseline tissue (archival tissue or a recent biopsy) and tissue obtained at disease progression (if sample is available). Further details on sample requirements and collection will be provided in the SRM.

7.7.2. Tumor Tissue

With the implementation of amendment 06, tumor samples will no longer be collected.

All enrolled subjects in the study will be required to submit a fresh tumor biopsy at screening in order to conduct retrospective tests for the identification and/or validation of known and novel biomarkers. Further details on sample requirements and collection will be provided in the SRM.

Optional on-treatment tumor biopsy samples will be analyzed using appropriate technologies including, but not limited to, RNAseq, exome or targeted DNA sequencing, IHC, and/or qRT-PCR.

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

7.7.3. Circulating cell free DNA/RNA Analysis

With the implementation of amendment 06, blood samples will no longer be collected.

Plasma isolated from blood collected at screening will be used to evaluate ESR1mutation status in circulating cell-free deoxyribonucleic (cfDNA) and/or RNA.

To further characterize the subject population, cfDNA and/or RNA measurements may be utilized to identify predictors of sensitivity or resistance to GSK525762 and fulvestrant in combination utilizing plasma isolated from blood at screening, on treatment and/or end of treatment.

7.8. Genetics

With the implementation of amendment 06, if a subject has consented for PGx research but the sample has yet to be collected, this will no longer be required.

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

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

7.9. Value Evidence and Outcomes

7.9.1. PRO-CTCAE

With the implementation of amendment 06, the PRO-CTCAE will no longer be completed.

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

7.9.2. EORTC-QLQ-C30 & EORTC-QLQ-BR23

With the implementation of amendment 06, the EORTC questionnaires will no longer be completed.

The effect of GSK525762 and fulvestrant, when given in combination, on symptoms and quality of life will be assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life questionnaires. Both the EORTC-QLQ-C30 (version 3) core questionnaire and the EORTC-QLQ-BR23 disease-specific modules will be administered.

8. DATA MANAGEMENT

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

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

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

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

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. Enrolment into the study is now closed as interim data failed to demonstrate meaningful clinical benefit in this patient population.

With the implementation of Amendment 06, specific assessments and collection of survival follow-up data will no longer be required. Please see Section 7.1 for further details. The study will conclude when the last subject has completed/discontinued study treatment and completed the end of treatment visit. There will be no Phase II.

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

9.1. Hypotheses

9.1.1. Phase I Safety

To evaluate for safety, Phase I will follow a mTPI design to identify the MTD of GSK525762 when administered in combination with fulvestrant. No formal statistical hypotheses will be tested. Analysis will be descriptive and exploratory. All data will be pooled, and descriptive analyses will be summarized and listed by dosing cohort at the end of Phase I. Dose escalation decisions will be based on the totality of clinical safety assessment data, as well as PK data.

9.1.2. Phase I Efficacy

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 objective response rate (CR + PR) of 25% relative to a 10% response rate suggesting no activity. This will be conducted by testing the null hypothesis that P0<=0.1 versus the alternative that P1

>0.25, 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 the measurable disease subjects only, defined as an objective response rate (CR + PR) of 20% relative to a 5% response rate suggesting no activity. This will be conducted by testing the null hypothesis that P0<=0.05 versus the alternative that 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 (AI Failure) and (0.005, 0.095) for Cohort 2 (CDK4/6+AI Failure) is used, which is equivalent to the information present in 0.1 subjects.

9.1.3. Phase II

In Phase II, the primary goal is to demonstrate a clinically meaningful improvement in PFS when GSK525762 is added to fulvestrant therapy. For this study, "clinically meaningful" is defined as a hazard ratio (HR) of 0.5, indicating that the combination therapy doubles the PFS relative to the comparator arm. A planned interim analysis will be performed when 45 subjects have progressed or died; the study may be stopped at that time for safety as well as for efficacy.

The primary objective of Phase II is to compare progression free survival (PFS) of the combinations of GSK525762 and fulvestrant therapy versus fulvestrant therapy alone in subjects with HR+/HER2- breast cancer.

Specifically, the study is designed to provide evidence with regard to PFS to support the null hypothesis:

$$H0: \lambda = 1$$

or to reject it in favor of the alternative hypothesis:

$$HA: \lambda < 1,$$

where λ is the hazard ratio: GSK525762 and fulvestrant / comparator.

The study will have 90% power to detect a hazard ratio (HR) of 0.5 with a one-sided 0.025 level test. Under the assumption of exponential PFS, this HR is equivalent to 100% increase in median progression-free survival for GSK525762 and fulvestrant versus comparator (11 months vs. 5.5 months). Refer to Appendix 3 for a discussion of the response assumptions used in the study.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

9.2.1.1. Phase I

Up to 35 measurable disease subjects per DL in Cohort 1 and 32 measurable disease subjects per DL in Cohort 2 may be enrolled to collect safety/tolerability, PK, PD, and efficacy data. Sixteen additional bone only disease subjects will be enrolled into DL1 cohort 2. Additional subjects may be enrolled at, or below the combination doses, in order to collect additional safety and PK data.

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

In Cohort 1 (AI Failure) the null and alternative hypotheses are:

H_0: ORR≤10%

H_A: ORR≥25%

When maximum sample size is 35, the design will have a Type I error (α) of 0.098 and 80% power.

In Cohort 2 (CDK4/6+AI Failure) the null and alternative hypotheses are:

H_0: ORR≤5%

H_A: ORR≥20%

When maximum sample size is 32, the design will have a Type I error (α) of 0.0535 and 81% power.

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

Simulation studies were conducted to evaluate the performance of the Bayesian design under various assumptions for the distribution of true ORRs across the cohorts. Operating characteristics including power, type I error, estimation of the ORR, and the probability of halting enrollment at interim analyses were assessed.

When the treatment effect is positive, the design maintains at least 80% power and type I error rate ≤0.09 on individual cohort. If both dose level are positive, the chance of advancing to phase 2 is as high as 94%. For more details, please see Section 9.4.10

9.2.1.2. Phase II

Phase II will enrol approximately 154 subjects with advanced or metastatic HR+/HER2- BC. The decision composition and dose of this cohort will be decided at the end of Phase I, and will depend on the totality data from Phase I as described in Section 4.3.

Based on available published data in treatment of metastatic ER+BC, the median PFS assumed for fulvestrant is approximately 5.5 months. Refer to Appendix 3, which details the clinical experience to date.

The following assumptions were made in the estimation of sample size and the required number of events for PFS for each of the two primary comparisons:

- Exponential distributions
- Constant accrual rate of 6 subjects per month in the first 6 months and 15 subject per month after
- 10% loss-to-follow-up rate
- A 1:1 randomization scheme
- Power of 90%

An overall of 2.5% one-sided risk of erroneously claiming benefit of the experimental arms over the control arm (comparator) in the case of no underlying difference between.

Seventy-seven (77) subjects per arm will be enrolled, leading to approximately 14 months of accrual. The first interim analysis for PFS will be performed when at least 45 PFS events (per RECIST v1.1) have occurred across GSK525762 in combination with fulvestrant and comparator arm (around 12 months after the first subject enrolled). The final analysis on PFS will be conducted when at least 90 PFS events (per RECIST 1.1) have been reported in GSK525762 combined with fulvestrant and comparator arm.

9.2.2. Sample Size Sensitivity

Sample size sensitivity assessments are described in Section 9.4.10.

9.2.3. Sample Size Re-estimation or Adjustment

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

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

The **Intent-to-Treat (ITT) population** will comprise all randomized subjects regardless of whether or not treatment was administered. This population will be based on the treatment to which the subject was randomized and will be the primary population for the analysis of efficacy and VEO data in Phase II.

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

All Evaluable Subjects will be defined as the study population used for decision-making at the interim futility analysis. Subjects who have at least two post-baseline radiological disease assessments or have progressed or died or permanently withdraw from the study treatment will be included in this population.

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

Additional analysis populations may be defined in the RAP.

9.3.2. Interim Analyses

9.3.2.1. Phase I

9.3.2.1.1. Dose Escalation and Safety Analyses

Once 3-10 subjects have been enrolled at each dose level, an interim analysis will be performed to determine if dose-escalation and/or dose expansion is appropriate. The primary driver for the dose escalation/expansion decisions in Phase I will be safety and tolerability of each dose cohort.

9.3.2.1.2. Efficacy Analyses

Interim analyses during expansion cohorts

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. Enrollment may be stopped early in any of the expansion cohorts for toxicity or lack of efficacy, should various criteria occur based on accrued data. The decision criteria for early stop for futility based on Bayesian Hierarchical model are described below. The decision will be made for each individual prior treatment history-specific cohort.

For the separate interim looks 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 response is observed in the first 10 enrolled evaluable subjects in that cohort or less than 2 confirmed responses are observed in the first 14 and 19 evaluable subjects in Cohort 1 and Cohort 2, respectively. The evaluable subject is defined as a subject, who has either progressed or died, withdrew from the study treatment, or is ongoing and has completed at least two post treatment disease assessments. For example, when there are 14 evaluable subjects available at the time of interim analysis with only one response, then the cohort may be stop for futility. Otherwise, the enrollment of the respective cohort will continue to the target sample size.

Futility interim analysis decision rules for the 10th to 34th evaluable subjects in Cohort 1 (AI Failure) and 10th to 32nd evaluable subjects in Cohort 2 (CDK4/6+AI Failure), specifying the number of subjects with a confirmed response needed for continuing enrolment or stopping for futility when total sample size is up to 35 in Cohort 1 (AI Failure) and up to 32 in Cohort 2 (CDK4/6+AI Failure) is presented in Table 7 and Table 9, respectively. These rules are intended as a guideline. Actual decisions will depend on the totality of the data.

Table 7 Decision Making Criteria for 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 8 Decision Making Criteria for 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

Additionally, the ORR and safety endpoints will be jointly assessed using a utility function when both DL1 and DL2 are safe and effective. The dose with the best utility function may be picked as RP2D for Phase 2. The details of the utility function calculations will be discussed in Reporting and Analysis Plan (RAP). This calculation is for guidance only, the final decision of RP2D will be based on totally of data.

The study population used for decision-making at the interim analyses on efficacy will be termed All Evaluable Subjects. Since disease assessments are to be completed every 8 weeks, subjects who have at least two post-baseline radiological disease assessments or have progressed or died or permanently withdraw from the study treatment will be included in this population. Interim analysis on safety will be conducted on all treated subjects.

Interim analyses at end of Phase I

Interim analyses of the data captured in Phase I may be undertaken for a given cohort/dose combination after each subject in the cohort/dose combination has had at least two post-baseline disease assessments or has progressed or died or withdrawn from

the study. Final analysis on Phase 1 PFS may be conducted when Phase 1 is completed. Data from the dose escalation and expansion cohort may be combined for some analyses, as appropriate.

9.3.2.2. Phase II

An IDMC will be utilized in this study to ensure external objective medical and statistical review of efficacy and safety data in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of IDMC data reviews and the scope of the IDMC reviews are described in the IDMC charter, which is available upon request.

The interim analyses for PFS will be performed for the purpose of evaluating whether to stop the trial early for futility or benefit in PFS.

"Futility" would correspond to declaring the GSK525762 in combination with fulvestrant arm be not better than the comparator arm in PFS.

Benefit: If a substantial prolongation in PFS is observed for the GSK525762 in combination with fulvestrant arm compared to the comparator arm, then consideration should be given to halting the trial due to observed benefit. Haybittle Peto method with a one-sided alpha of 0.0001 for PFS in favor of the experimental arm will serve as a guideline for potential benefit. Observation of substantial benefit as described above would signal further examination of available data by the IDMC, with consideration of altering the conduct, or terminating the study.

For the purpose of evaluating whether to stop the trial due to futility, a Gamma family beta spending function with a parameter of -0.5 will be utilized. The boundary does not represent a binding decision to stop the trial should this boundary be crossed. The boundaries are defined in EAST to preserve Type I error at 2.5% under the assumption of a non-binding futility rule.

The EAST software package will be used to calculate the appropriate bounds at the time of the analyses, given the fraction of information available. Assuming an accrual time of 14 months and a follow-up time of 6 months and the accrual rate is 6 subjects per month in the first 6 months and 15 subjects per month after, the time point of interim analyses is around 13 months. An example of the nominal significance levels corresponding to the error spending functions as well as planned stopping boundaries and decision rules in terms of hazard ratios for the analysis time points of progression free survival, are as follows:

- 50% of expected events: stop for futility if HR>0.9247, stop for efficacy if HR<0.33
- 100% of expected events: α=0.025, claim superiority of the experimental arm if HR<0.66

At the interim analysis, if GSK525762 in combination with fulvestrant demonstrates no difference from the comparator arm, enrollment may be halted. The IDMC may also recommend halting the trial based on accruing safety information.

9.3.3. Final Analysis

For Phase II, final analyses may be conducted when sufficient PFS events (90) have accrued for comparison of the combination arm with the comparator.

9.4. Key Elements of Analysis Plan

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

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

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

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

Demographic and baseline characteristics will be summarized.

9.4.1. Safety Analyses

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

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

9.4.2. Extent of Exposure

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

9.4.3. Adverse Events

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

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

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

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

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

9.4.4. Clinical Laboratory Evaluations

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

9.4.4.1. Other Safety Measures

Data for vital signs, electrocardiograms (ECGs), and echocardiograms (ECHOs) or multigated acquisition scan (MUGA) will be summarized based on predetermined criteria identified to be of potential clinical concern. Further details will be provided in the RAP.

9.4.5. Pharmacokinetic Analyses

9.4.5.1. Pharmacokinetic Parameters

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

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

- maximum observed plasma concentration (Cmax)
- time to Cmax (tmax)
- trough concentration (Cτ)

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

9.4.5.2. Statistical Analysis of Pharmacokinetic Data

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

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

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

9.4.6. Pharmacokinetic/Pharmacodynamic Analyses

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

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

Overall efficacy data, as assessed by conventional RECIST 1.1 criteria (best confirmed response) may be described using ordered categorical model and/or continuous models with summary exposure parameters (e.g.; Cmax, Ctrough, and Cav) as covariates derived from the population PK analysis. Further model details will be provided in the RAP.

9.4.7. Tumor Kinetics Analysis

Data from Phase I and Phase II of the study may be combined to describe the kinetics of tumor growth based on the sum of longest diameters of target lesions.

The kinetics of tumor growth may be described as a function of time using the Non Small cell lung cancer (NSCLC) model described by the FDA [Wang, 2009]. The tumor size (TS) is expressed as:

$$TS(t) = BSL \bullet e^{-SRt} + PR \bullet t$$

where TS(t) denotes the tumor size measured as the sum of longest distance (mm) of lesions or volume (mm3) at time t, BSL is the baseline tumor size, SR is the exponential tumor shrinkage rate constant and PR is the linear tumor progression rate.

The kinetics of tumor growth may also be described as a function of time using the model described by Claret [Claret, 2009]. The model is expressed as:

$$dTS(t)/dt = (KL - KD \bullet e^{-\lambda t}) \bullet TS(t)$$

where TS(t) denotes the sum of longest distance (mm) of lesions or volume (mm3) at time t, with TS(0) being the baseline tumor size, KL represents the exponential tumor growth rate, KD represents the exponential rate of tumor shrinkage (i.e. drug effect on total tumor size), λ is the rate constant for drug resistance/disease progression. A measure of exposure of one or more of the administered medications may be included in the models.

The equation proposed by Wang and/or Claret may be fit to the observed data using a mixed-effects model with NONMEM VII. Other models of the kinetics of tumor growth, such as a 2-parameter model, may be used to analyze the data [Stein, 2011; Stein, 2012].

The time to tumor growth (TTG) may be estimated with parameters from the appropriate model. Subject characteristics such as baseline tumor size, performance status, lactate dehydrogenase (LDH), age, sex, race, prior therapies, or radiotherapy, may be evaluated to determine which covariates have a significant effect on the kinetics of tumor growth.

Relationship between tumor growth marker and clinical activity measured may be explored as well.

9.4.8. Efficacy Analyses

9.4.8.1. Phase I

For the Phase I final analysis, each dose and cohort will be analyzed separately. In Cohort 2 (CDK4/6+AI Failure), measurable disease subjects and bone only disease subjects will be analyzed separately and combined within a dose. However, bone only disease subjects will not be evaluated for ORR. The focus of analyses that contain bone only disease subjects will be DCR, PFS and OS.

The overall response (ORR) rate is defined as the percentage of subjects with a confirmed complete response (CR) or a partial response (PR) at any time as per RECIST 1.1 (Appendix 7). The disease control rate (DCR) is defined as the percentage of subjects with a confirmed CR, PR, or stable disease (SD) ≥6months as per disease-specific criteria (Appendix 7). Subjects with unknown or missing response will be treated as non-responders, i.e. these subjects will be included in the denominator when calculating the percentage. The number and types of responses, as outlined in RECIST 1.1, will be listed and summarized separately, as appropriate.

The observed confirmed and unconfirmed ORR will be reported at the interim and final analysis for each cohort specified in Phase 1 treated dose, if data warrant. The estimates along with 95% exact confidence interval (CI) will be provided. Bayesian inference based on summary statistics from the posterior distributions of each ORR will be reported at interim and final analyses. The posterior mean and posterior 2.5% and 97.5% percentiles of the ORR will be calculated for each cohort. In addition, the posterior probability that the ORR exceeds its corresponding historical control will be reported for each cohort.

The ORR differences of the same cohort between two doses will be provided along with corresponding 95% CI. A chi-square test will be used to test for differences between doses if data warrant.

Duration of response is defined as the subset of subjects who show a confirmed CR or PR, the time from first documented evidence of CR or PR until the first documented sign of disease progression or death. Duration of response will be summarized descriptively for each cohort, if data warrant, using Kaplan-Meier medians and quartiles. Details on rules for censoring will be provided in the RAP.

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

For the analysis of **overall survival (OS)**, the last date of known contact will be used for those subjects who have not died at the time of analysis; such subjects will be considered censored. Further details on rules for censoring will be provided in the RAP. If data warrant, OS will be summarized by cohort and dose level specified in Phase I using Kaplan-Meier quantile estimates along with 2-sided 95% CIs at the time of end of Phase 1 interim analysis.

9.4.8.2. Phase II

PFS along with 95% confidence interval for each treatment will be estimated using the Kaplan Meier method and treatment comparisons will be made using a log-rank test (defined in Section 9.1.3). The median PFS for each treatment, the hazard ratio for each comparison along with 95% confidence intervals will be reported.

PFS will be defined as the time from randomization until the first date of either disease progression or death due to any cause and will be evaluated for the combination versus

the comparator. The date of objective disease progression will be defined as the earliest date of disease progression as assessed by the investigator using RECIST 1.1. For subjects who have not progressed or died at the time of the PFS analysis, censoring will be performed using the date of the last adequate disease assessment. In addition, subjects with an extended loss to follow-up or who start a new anti-cancer therapy prior to a PFS event will be censored at the date of the last adequate disease assessment prior to the extended loss to follow-up or start of new anti-cancer therapy, respectively. Further details on censoring rules will be outlined in the RAP.

Additional sensitivity and/or subgroup analyses for PFS may be pre-specified in the RAP, if appropriate.

The ORR will be tabulated based on number and percentage of subjects attaining either a confirmed or unconfirmed overall best response of CR or PR in the ITT population in Phase II. The DCR will also be tabulated based on number and percentage of subjects attaining a confirmed CR, PR, or stable disease (SD) ≥ 6 months in the ITT population in Phase II. Per RECIST 1.1., subjects with unknown or missing response data, including those who withdraw from the study without an assessment, will be treated as non-responders (i.e., they will be included in the denominator when calculating the percentage). No imputation will be performed for missing lesion assessment or tumour response data.

OS along with 95% confidence interval for each treatment will be estimated using the Kaplan Meier method and treatment comparisons will be made using a log-rank test. All cause mortality will be used and censoring will be performed using the date of last known contact for those who are alive or lost to follow-up at the time of analysis. The hazard ratio along with 95% confidence intervals will be provided for each of the comparisons. Sensitivity analyses to ascertain the effect of baseline prognostic factors may be performed. Details will be provided in the RAP.

Overall response rates (ORR) for each treatment group as well as for differences between the arms will be provided along with corresponding 95% CI. A chi-square test will be used to test for differences between treatment arms.

9.4.9. Other Analyses

9.4.9.1. Translational Research Analyses

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

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

9.4.9.2. Novel Biomarker(s) Analyses

The results of these biomarker investigations, including correlation between ESR1 mutations and clinical response, will be reported separately from the main clinical study

report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

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

9.4.9.3. Pharmacogenetic Analyses

Further details on pharmacogenetic (PGx) analyses will be addressed in Appendix 11 and the PGx RAP.

9.4.10. Simulations and Design Operating Characteristics

9.4.10.1. Simulation Description

Extensive simulations have been conducted to develop and understand the performance of the seamless design, interim monitoring, and decision criteria.

9.4.10.2. Software Details

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

9.4.10.3. Trial Sample Size and Simulation Scenarios

Sample size requirements for halting enrollment at interim analyses for simulations is based on the number of subjects enrolled; while in practice, they will be based on the number of subjects with available response data. This discrepancy is due to software feasibility, but should not have a significant impact on operating characteristics of the design. Simulations assumed the first interim analysis occurring once 10 evaluable subjects in the same cohort at the same dose level have been enrolled. An average of 4 subjects per month per cohort is assumed. The time from subject entry until the confirmed response assessment was performed is assumed to be 12 weeks. For each dose, a maximum 10 subjects will be assigned to the dose escalation stage and if that dose is safe to expand, a maximum of 35 subjects will be assigned to each cohort.

Although actual enrollment may vary, the estimated enrollment rate of 4 subjects per month per cohort is incorporated into the simulations. The real enrollment rate may vary from the assumed enrollment rate in simulation, but should not impact on operating characteristics of the design. Simulation scenarios and design characteristics for one cohort on two dose levels DL1 and DL2 are listed in Table 9 under 1000 simulations. The DLT rates and ORR listed are listed in the order of DL1 and DL2.

Table 9 Simulation Scenarios and Design Characteristics for One cohort

Scenarios (DL1 DL2)	<= MTD (%)		Declare Efficacious if safe (%)		Advance to phase 2 (%)			Average N		Early termination due to futility (%)	
DLT rates/ ORRs	**DL1**	**DL2**	**DL1**	**DL2**	**DL1**	**DL2**	Any dose	**DL1**	**DL2**	**DL1**	**DL2**
0.1, 0.2 /0.1,0.1 Safe/Null	98.2	88.8	7.13	11.04	7.0	9.8	16.3	24.76	21.66	62.73	52.15
0.1, 0.2 /0.1,0.25Safe/ one posi	97.80	89.5	9.1	82.79	8.9	74.1	78.3	25.03	28.05	59.92	5.47
0.1,0.2 /0.25,0.25 Safe/ Posi	97.5	87.5	83.08	81.14	81	71	92.4	32.24	27.7	7.49	7.77
0.2, 0.4 /0.25,0.25 One safe/ Posi	90.1	40.7	80.47	83.78	72.5	34.1	79.3	27.69	10.36	5.77	5.16
0.2, 0.4 /0.25,0.4 One safe/ Posi	89.6	41.3	81.58	96.61	73.1	39.9	79.3	26.85	10.53	5.92	0.24
0.3, 0.4 /0.25,0.25 MTD, Toxi/ Posi	71.3	25.1	79.38	79.88	56.6	19.8	60	19.54	6.09	5.47	6.77

9.4.10.4. Operation Characteristics

The probability of declaring efficacy within an individual cohort if the dose is declared safe (power and type I error rate) per dose are examined across scenarios for the distribution of assumed true DLT rates and ORRs for each dose in one cohort. Similar results are expected for the other two cohorts. The power is the probability declaring efficacy when the true underlying ORR is larger than its corresponding historical control 0.1. Type 1 error rate is the probability of declaring efficacy within an individual cohort when the true underlying response rate is equal to the historical control.

The power and type I error rate on individual dose level are calculated if the dose is determined to be safe. In the simulations that a particular dose is declared over MTD, it won't be included in the calculation. When the dose is efficacious, the design maintains at least 80% power. The type I error rate is controlled to <0.11.

9.4.10.5. Stopping Early

Table 9 also presents the proportion of trials that halt enrollment early for futility across simulation scenarios if expansion cohort starts. Since the study requires at least 10 evaluable subjects in a particular cohort at the same dose prior to stopping early for futility, the ability for a cohort to stop early is largely dependent upon the projected maximum sample size and enrollment rate per cohort.

Non-responsive cohorts stop early for futility between 50% and 63% of the time. Responsive cohorts generally have lower than 9% chance stop early for futility.

9.4.10.6. Mean Proportion of advancing to Phase 2

To evaluate the design performance in making the decision of advancing to Phase 2, Table 9 listed the probabilities of advancing any or both of the two doses to Phase 2 after Phase 1. In the scenario where both DLs are safe and positive, there is a 92.4% chance that at least one dose will be picked for Phase 2. When both dose levels are safe but not positive, there is 16% chance that at least one dose will be picked for Phase II.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

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

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

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

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent

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

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

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

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

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

10.4. Quality Assurance

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

In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant

documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

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

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

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

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

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

10.6. Records Retention

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

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

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

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

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

requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.

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

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

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

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate. GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis

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

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ACLS	Advanced Cardiac Life Support
AE	Adverse Event
AI	Aromatase Inhibitor
ALP	Alkaline phosphatise
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé
aPTT	Activated Partial Thromboplastin Time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
BAL	Bronchoalveolar lavage
BC	Breast Cancer
BCRP	Breast Cancer Resistance Protein
BET	Bromodomain and extra-terminal
BID	*Bis in die* - Twice daily
BLRM	Bayesian logistic regression model
BNP	B-type Natriuretic Peptide
CAP	College of American Pathologists
Cav	Average observed concentration
CBC	Complete blood count
CDK	Cyclin-Dependent Kinase
CI	Confidence Interval
CK	Creatine kinase
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacokinetics Modelling & Simulation
CR	Complete response
CRF	Case record form
CRO	Contract Research Organization
CT	Computerized Tomography
CV	Cardiovascular/ Coefficient of variance
CYP	Cytochrome P
$C\tau$	Pre-dose (trough) concentration at the end of a dosing interval
D	Day
DAP	Data Analysis Plan
DCR	Disease control rate
DHEA	Dehydroepiandrosterone

dL	Deciliter
DL	Dose Level
DLCO	Diffusing Capacity of the Lung for Carbon Monoxide
DLT	Dose limiting toxicity
DMPK	Drug Metabolism and Pharmacokinetics
DNA	Deoxyribonucleic acid
DPM	Dirichlet Process Mixtures
DRE	Disease-related event
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of the treatment
ER	Estrogen Receptor
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FSH	Follicle Stimulating Hormone
FTIH	First time in human
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GI	Gastrointestinal
GCSF	Granulocyte Colony-Stimulating Factors
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C Virus
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HepC	Hepatitis C
HIV	Human Immunodeficiency Virus
HPLC	High pressure liquid chromatography
hPXR	Human Pregnane X receptor
hr	Hour(s)
HR	Heart rate/Hazard Ratio
HR+HER2-	Hormone Receptor-positive, HER2-negative
HRT	Hormone replacement therapy
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent data monitoring committee
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee

Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
IM	Intramuscularly
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
IVD	*In vitro* companion diagnostic device
Kg	Kilogram
L	Liter
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LHRH	Luteinizing hormone-releasing hormone
LLN	Lower limit of normal
LMWH	Low molecular weight heparin
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MFD	Maximum feasible dose
mg	Milligrams
Mins	Minute(s)
mL	Milliliter
MM	Medical Monitor
mmHg	Millimeter of Mercury
mmol	Millimole
MR	Minimal Response
MRI	Magnetic resonance imaging
mRNA	Messenger Ribonucleic acid
MSDS	Material Safety Data Sheet
MSDS	Material Safety Data Sheet
msec	Milliseconds
MTD	Maximally-tolerated dose
mTOR	Mammalian Target of Rapamycin
mTPI	Modified toxicity probability interval
MUGA	Multigated Acquisition Scan
NA	Not Applicable
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	Not Evaluable
NSCLC	Non Small cell lung cancer

NT-proBNP	N-terminal pro–B-Type natriuretic peptide
NYHA	New York Heart Association
OAT1	Organic anion transporter 1A1
OAT3	Organic anion transporter 3
ORR	Overall response rate
OS	Overall survival
P2D	Part 2 Dose
PCR	Polymerase chain reaction
PD	Pharmacodynamic/Progressive Disease
PET	Positron emission tomography
PFS	Progression free survival
Pgp	P-glycoprotein
PGx	Pharmacogenetics
PI	Principal Investigator
PK	Pharmacokinetic
PR	Partial response
PRO-CTCAE	Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events
PS	Performance status
PT	Prothrombin time/ Preferred (coded) term
PTT	Partial thromboplastin time
QD	*quaque die* - Once daily
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Part 2 Dose
RR	Time interval from the onset of one QRS complex to the onset of the next QRS complex/Response Ratio
SAE	Serious adverse event(s)
SCLC	Small cell lung cancer
SCR	Screening Visit
SD	Stable disease/ Standard deviation
SERD	Selective Estrogen Receptor Degrader
SoC	Standard of Care
SRM	Study Reference Manual
SRT	Safety Review Team
$t_{1/2}$	Apparent terminal half-life
T3	Free triiodothyronine
T4	Free thyroxine
TID	Three times daily
Tmax	Time of maximum concentration
TNF	Tumor Necrosis Factor
TS	Tumor size
TSH	Thyroid stimulating hormone
TTG	Time to tumor growth

TTP	Time to progression
ULN	Upper limit of normal
USA	United States
W	Week
WBC	White blood cells

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
EAST
MedDRA

12.2. Appendix 2: Management of Suspected Toxicity

The following dose modification criteria in Table 10 should be used to provide guidance, but not act as a replacement for sound clinical judgment. If a given toxicity is considered by the investigator to be related to a single investigational drug and not both, then dose modification may only occur with the drug associated with a specific toxicity or event of clinical concern.

Table 10 Dose Adjustment/Stopping Safety Criteria

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

Toxicity	**Dose Adjustment/ Stopping Criteria**	**Management Guidelines[c]**
QTcF	If ≥ 60 msec change from baseline occurs AND QTcF ≥500 msec OR QTcF ≥530 msec And <60 msec change from baseline (average of three ECGs over at least 15 minutes)	Discontinue GSK525762 and notify the Medical Monitor. • Evaluation by cardiologist • Supplement electrolytes to recommended levels: a. Maintain serum potassium > 4mol/L b. Maintain serum magnesium levels >0.85 mmol/L • Rule out other potential etiologies for prolonged QTcF such as cardiac ischemia • Discontinue any concomitant medications with potential for QTcF prolongation. • 24-hour telemetry monitoring if clinically indicated. This subject may consider starting study treatment at a one dose level reduced if all of the following criteria for QTcF re-challenge are met. If approval for re-challenge is granted, the subject must be re-consented (with a separate informed consent specific to QTc prolongation) (1) QTcF reduced to <480 msec, (2) Potassium and magnesium levels are within institutional normal range, (3) A favorable risk/benefit profile (in the medical judgement of the Investigator and the Medical Monitor), (4) Approval within GSK medical governance: a. agreement with SERM MD and PPL, b. review with Chair or co-Chair of the GSK QT panel, c. SERM VP and Clinical VP approval d. Head Unit Physician approval (5) The subject is re-consented regarding the possible increased risk of QTc prolongation. • Discontinuation procedures: If the subject is withdrawn due to QTcF event, the subject should complete the following activities post-dose: (1) Evaluation by cardiologist. (2) Weekly assessments for QTcF until ≤30 msec change from baseline reached, and then next assessment at 4 weeks post-dose. (3) If QTcF results have not resolved to baseline by 4 weeks post-dose, then continue every 4-5 weeks until resolution
Troponin	Troponin level >ULN	Contact the subject immediately for evaluation of symptoms and to obtain ECG. Repeat troponin as soon as possible (ideally within 24-48 hours).

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines[c]
		For asymptomatic subjects with repeat troponin values >ULN, hold study medication(s), refer to a cardiologist and contact the Medical Monitor. If the repeat value is within the normal range, the subject may continue study medication with close follow-up for symptoms, ECG monitoring and further troponin measurements as clinically indicated. If the subject is symptomatic or the troponin level approaches the threshold for MI according to local lab parameters, the study medication must be permanently discontinued and the subject will be referred immediately to a cardiologist for appropriate medical care.
LVEF	Asymptomatic, absolute decrease of >10% in LVEF compared to baseline and the ejection fraction is below the institution's lower limit of normal (LLN)	• Interrupt investigational drug(s) and repeat evaluation of LVEF within 2 weeks • If LVEF recovers (defined as ≥LLN and absolute decrease ≤10% compared to baseline) at any time during the next 4 weeks, after consultation and approval of the Medical Monitor, the subject may be restarted on investigational drug(s) at a reduced dose. Monitoring to be performed at 2 and 4 weeks after restarting investigational drug(s) and then per protocol specifications. • If LVEF does not recover within 4 weeks, permanently discontinue investigational drug(s). Evaluation by a cardiologist will be conducted. Ejection fraction should continue to be monitored at 2 weeks, 4 weeks and every 4 weeks until 16 weeks or resolution whichever is longer.
	Grade 3 or 4	• Permanently discontinue investigational drug(s). Evaluation by a cardiologist will be conducted. Ejection fraction should be monitored at 2 weeks, 4 weeks and then every 4 weeks until 16 weeks or resolution whichever is longer.

Toxicity	**Dose Adjustment/ Stopping Criteria**	**Management Guidelines[c]**
Liver	• ALT ≥5X ULN, OR • ALT ≥3X ULN plus either bilirubin ≥2X ULN (>35% direct bilirubin, bilirubin fractionation required) or INR >1.5 without evidence of biliary obstruction or progressive disease, OR • ALT ≥3X ULN plus symptoms of liver injury or hypersensitivity[a]	Refer to Section 5.4.1 for liver chemistry stopping criteria and treatment algorithms, and to Appendix 8 for reporting and follow-up of suspected liver events.
	Elevated bilirubin, hypoalbuminemia, prolonged PT, ascites, and/or encephalopathy	Refer to Appendix 13 for definition of Child-Pugh score • Child-Pugh Class A: No change to fulvestrant dose required • Child-Pugh Class B: Reduce dose of fulvestrant to 250 mg, administered as per the standard schedule. Fulvestrant dose may be re-escalated to 500 mg once liver function improves. • Child-Pugh Class C: Hold fulvestrant until liver function has improved In addition, please refer to "other non-hematologic toxicity", below, for management of GSK525762
	Elevated bilirubin without other evidence of liver injury	Refer to "other non-hematologic toxicity", below

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines[c]
Hypo- and Hyperglycemia (for management purposes, refer to mild, moderate and severe intensity criteria; however for CRF reporting use NCI-CTCAE v4.0 [NCI, 2009] grading system)	Fasting blood glucose >150 mg/dL to 250 mg/dL (Mild hyperglycemia)	• Monitor fasting and preprandial glucose. • If persistant over 2 repeats over 3-4 weeks, consult Diabetologist, consider starting metformin
	Fasting blood glucose any blood glucose >250 mg/dL (Moderate to Severe hyperglycemia)	• Hold investigational product(s) and instruct subject to notify investigator immediately. • Monitor for ketoacidosis as clinically indicated. • If subject has evidence of ketoacidosis, initiate prompt therapy. Antihyperglycemic therapy with insulin is preferred. Consult Diabetologist/Endocrinologist. Careful monitoring should be performed to control for rebound hypoglycemia as effect of investigational product(s) resolve • May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with Medical Monitor.
	Fasting blood glucose <70 mg/dL (Moderate to Severe hypoglycemia)	• Hold investigational product(s) • Provide sugar containing liquids and monitor blood sugar closely. Check for insulin and c-peptide levels. After blood sugar normalizes • Restart study treatment one dose level lower if the hypoglycemia cannot be attributed to any other cause, and fasting blood sugar will be monitored on a daily basis until the blood glucose level is stabilized.
Diarrhea	Grade 1	• Initiate supportive care including loperamide.
	Grade 2	• Initiate supportive care including loperamide. Consider temporary discontinuation of study medications and discuss with Medical Monitor.
	Grade 3 or 4	• Above plus consider IV hydration, hospital admission and prophylactic antibiotics as appropriate. Withhold study drug until diarrhea has resolved to ≤Grade 1, continue diarrheal prophylaxis. • Restart study treatment one dose level lower

Toxicity	**Dose Adjustment/ Stopping Criteria**	**Management Guidelines[c]**
Mucositis	Grade 1-2	• Encourage oral hygiene. Offer topical supportive anesthetics. Encourage adequate hydration.
	Grade 3-4	• (Above plus systemic opiate administration as needed.) Consider IV hydration and hospital admission as appropriate. • For mucositis ≥ Grade 3, hold GSK525762 until mucositis is **≤ Grade 1** and resume the same dose of GSK525762. If **mucositis** ≥ Grade 3 recurs, hold GSK525762 until mucositis is **≤ Grade 1**, then reduce GSK525762 one dose level. If mucositis ≥ Grade 3 recurs a third time at reduced dose, hold GSK525762 until mucositis resolved to ≤ Grade 1, then reduce GSK525762 one dose level (if possible) or discontinue permanently.
Pneumonitis	Grade 1	• (For all Grades) Obtain high resolution chest CT. Consider evaluation by pulmonologist. Consider room air O2 saturation at rest via weekly room air pulse oximetry reading (X 2, 5 mins apart). • If any decline is observed in O_2 saturation, hold study drug, repeat chest x-ray to determine if progression of pneumonitis has occurred and consult pulmonologist.
	Grade 2	• Hold investigational drug(s) until recovery to ≤ Grade 1, then reduce dose by at least 25%. Discontinue investigational drug(s) if no recovery to ≤ Grade 1 within 4 weeks. • Must be evaluated by a pulmonologist. Perform pulmonary function tests including: spirometry, Diffusing Capacity of the Lung for Carbon Monoxide (DLCO), and weekly room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). Repeat evaluations every 4 weeks until pneumonitis has resolved. Consider a bronchoscopy with biopsy and/or bronchoalveolar lavage (BAL). • Treat only if symptomatic. Consider corticosteroids if symptoms are troublesome and infectious origin is ruled out. Taper as medically indicated.
	Grade 3 and 4	• Discontinue investigational drug(s). • Evaluation by pulmonologist required. • Required pulmonary function tests including: spirometry, DLCO, and weekly room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). Repeat evaluations at least every 8 weeks until return to normal. Bronchoscopy with biopsy and/or BAL is recommended. • Consider treatment with corticosteroids in the appropriate clinical setting and in consultation with the pulmonologist (1-2 mg/kg of prednisone [or

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines[c]
		equivalent] IV once daily) if infectious origin is ruled out. Taper over 4-6 weeks.
Other non-hematologic toxicity (except those listed in Section 4.2.3.5)	Grade 1	• No change in dose
	Grade 2	• For drug-related Grade 2 toxicities, continue dosing with no change or may consider holding for up to 1 week for toxicity to be < Grade 2. Continue at the same dose (dose reduction is required if the grade 2 toxicity is considered a DLT)
	Grade 3	• Hold dose until toxicity is ≤Grade 1, then restart with no change for 1st episode. Reduce by one dose level with 2nd episode if recovery to ≤Grade 1 within 21 days. If no recovery to ≤Grade 1 after a 21-day delay in the 2nd episode, subject should be permanently discontinued.
	Grade 4	• In patients with objective evidence of clinical benefit, hold therapy until toxicity is ≤Grade 1, then restart with one dose level lower. If the same Grade 4 non-hematological toxicity recurs, study drug will be permanently discontinued.

a. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)

b. These guidelines are for suspected drug associated fever; please perform any additional tests as clinically appropriate for other causes of fever such as infection.

c. Fulvestrant should be restarted following the original schedule.

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

12.3. Appendix 3: Rationale for Response Assumptions

The Bayesian statistical design utilized in the dose expansion cohort(s) in Phase I of the study will test the hypothesis that the combination of GSK525762 and fulvestrant will achieve a clinically meaningful response rate, versus the null hypothesis that the combination will achieve a response that is no better than historical controls. The null and alternative hypotheses were determined based on historical response rates (including fulvestrant as a single agent).

For Phase II of the study, the design will test the hypothesis that the combination of GSK525762 and fulvestrant will achieve a clinically meaningful improvement in progression-free survival when compared against either fulvestrant alone or to the currently approved standard of care.

When determining appropriate efficacy hurdles, the following factors were taken into account:

- It is unlikely that the combination of GSK525762 and fulvestrant will be further combined with additional targeted therapy or chemotherapy. Therefore, the efficacy of the combination will need to outperform the current standard of care for this population.

- The effect of the two drugs in combination must yield a higher response rate than fulvestrant alone in order to justify the potential additional toxicity and burden of a second medication. Furthermore, since both drugs are likely to have some efficacy as single agents, the efficacy bar must be set significantly higher for the combination to mitigate the risk that any observed clinical activity is due primarily to only one component of the combination rather than both drugs given in combination.

- The combination of GSK525762 and fulvestrant should perform at least as well as, if not better than, any combination of fulvestrant with other targeted therapy or with conventional chemotherapy in order to justify its use in combination.

- The efficacy bar is set higher than any second or third-line drugs in order to evaluate whether GSK525762 plus fulvestrant represents a clinical benefit over the standard of care.

12.3.1. Phase 1

The statistical design in the dose expansion portion of this study is based upon the hypothesis that the historical ORR of relapsed/refractory HR+/HER2- BC is 10%. Multiple large clinical trials have demonstrated an ORR of approximately 8-10% when fulvestrant alone is administered in the second line and later to patients previously treated with aromatase inhibitors [Chia, 2008, Di Leo, 2010, Cristofanilli, 2016]. Therefore, a historical value of 10% would suggest that GSK525762 plus fulvestrant was performing no better than fulvestrant alone in this population.

Furthermore, a null hypothesis of 0.1 would suggest that the combination would perform at least as well as other combinations currently used in clinical practice. A comparable response rate (12.6%) was observed when everolimus was combined with exemestane in women who had previously failed AI therapy [Baselga, 2012].

Currently, the most robust ORR observed in line 2+ for ER+BC is from the combination of palbociclib plus fulvestrant. In the pivotal PALOMA3 trial [Cristofanilli, 2016], an ORR of almost 25% was observed among women who had measurable disease at baseline. This value, however, was not chosen as the historical response rate for the following reasons: First, palbociclib has not been approved as a SoC worldwide at the time of this trial; as a consequence, palbociclib (and thus these potential results) are not available to all subjects who may enroll on this study. Second, for women who have progressed on a combination of palbociclib and fulvestrant (who could be enrolled into the current study), there are no data to support a historical response rate of more than 10%.

In order to detect a clinically meaningful response rate as described in Section 12.3, a target ORR of 25% was selected. This represents a more than doubling of the historical rate, and also matches the ORR observed in the palbociclib/fulvestrant combination [Cristofanilli, 2016]. Furthermore, it exceeds the ORR observed with any other single-agent endocrine therapy in later lines [Robertson, 2003, Chia, 2008], as well as the other approved combination, everolimus plus exemestane [Baselga, 2012].

12.3.2. Phase 2

The statistical design in Phase 2 of this study is based upon the hypothesis that the combination of fulvestrant plus GSK525762 will double the PFS (i.e., a hazard ratio of 0.5) compared to fulvestrant alone (for subjects previously treated with AI and/or CDK4/6 inhibitor/AI) or compared to SoC (for subjects previously treated with CDK4/6 inhibitor/fulvestrant). This value is comparable to the PFS improvement identified in the palbociclib/fulvestrant study (HR=0.46; [Cristofanilli, 2016] as well as the everolimus/exemestane study (HR=0.43; [Baselga, 2012]).

12.3.3. References

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12.4. Appendix 4: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

12.4.1. Contraception Guidance:

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

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

1. Non-hormonal intrauterine device (IUD) or intrauterine system (IUS) that meets the ≤1% failure rate as stated in the product label
2. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

Note: Hormonal methods of contraception are not permitted since the efficacy of these methods in combination with GSK525762 has not been assessed. LHRH-acting agents alone are not considered an adequate form of contraception. GSK525762 has been shown to effect female reproductive systems in animals, therefore women of childbearing potential should adhere to this contraceptive guidance whilst on study and for 7 months after cessation of treatment with GSK525762, to be in line with GSK525762 guidance. **Effective January 13, 2020, the EU fulvestrant Summary of Product Characteristics was updated to include effective contraceptive use for women of childbearing potential for 24 months post last dose. Please consult the local fulvestrant prescribing information to ensure subjects are using effective forms of contraception for the appropriate length of time required after stopping treatment with fulvestrant.**

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

12.4.2. Collection of Pregnancy Information

Any female subject who becomes pregnant while participating will be withdrawn from the study.

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a subject's pregnancy.

- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 10. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

12.4.3. References

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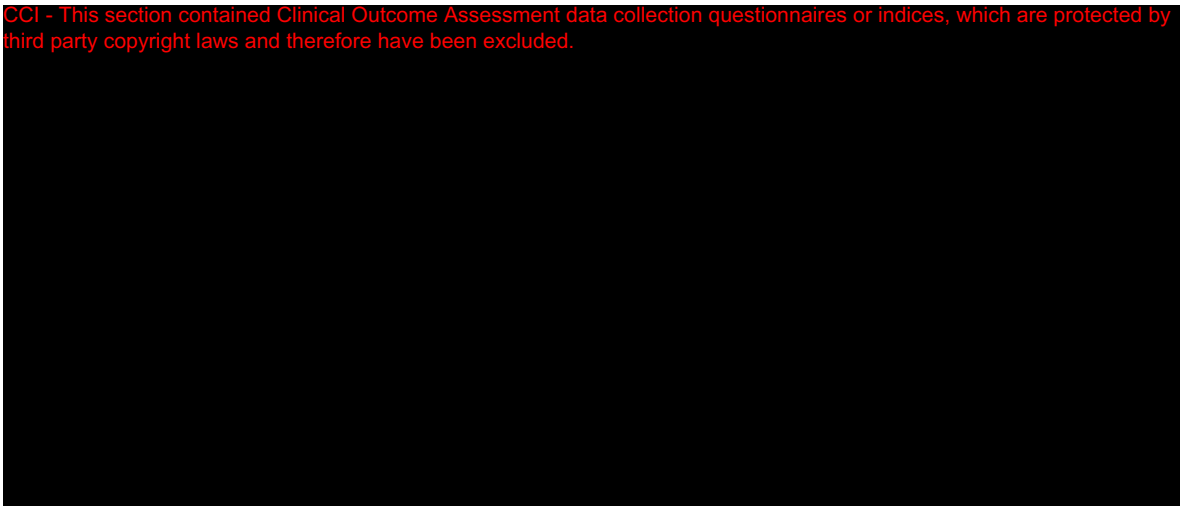
12.5. Appendix 5: ECOG Performance Status

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

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.



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12.6. Appendix 6: Cockcroft and Gault Method for Calculated Creatinine Clearance

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

[Cockcroft, 1976]

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12.7. Appendix 7: Guidelines for Assessment of Disease, Disease Progression and Response Criteria – adapted from RECIST 1.1 [Eisenhauer, 2009]

12.7.1. Baseline Documentation of Target and Non-Target Lesions

- All baseline lesion assessments must be performed within 28 days of randomization.
- Lymph nodes that have a short axis of <10mm are considered non-pathological and should not be recorded or followed.
- Pathological lymph nodes with <15mm and but ≥10mm short axis are considered non measurable.
- Pathological lymph nodes with ≥15mm short axis are considered measurable and can be selected as target lesions, however lymph nodes should not be selected as target lesions when other suitable target lesions are available.
- Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

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

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

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered measurable. Bone scans, FDG-PET scans or X-rays are not considered adequate imaging techniques to measure bone lesions.
- All other lesions (or sites of disease) should be identified as non-target and should also be recorded at baseline. Non-target lesions will be group by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.
- The following are required at baseline: CT for Chest/Abdomen/Pelvis or MRI for Abdomen/Pelvis (in combination with a non-contrast enhanced CT of the Chest) as described in Section 7.2.1. At each post baseline assessment, evaluations of the sites of disease identified by these scans are required.

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

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

Assessment Guidelines

Please note the following:

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

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

CT and MRI: **Contrast enhanced CT with 5mm contiguous slices is recommended.** Minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimised for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible, the same scanner should be used [Eisenhauer, 2009].

X-ray: In general, X-ray should not be used for target lesion measurements owing to poor lesion definition. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung; however, chest CT is preferred over chest X-ray [Eisenhauer, 2009].

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

Guidelines for Evaluation of Disease

Measurable and Non-measurable Definitions

Measurable lesion:

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

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

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

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

Non-measurable lesion:

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

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

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

Response Criteria

Evaluation of target lesions

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

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

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

Note:

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

Evaluation of non-target lesions

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

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

- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.
- Not Applicable (NA): No non-target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Note:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- In the presence of non-measurable only disease consideration should be given to whether or not the increase in overall disease burden is comparable in magnitude to the increase that would be required to declare PD for measurable disease.
- Sites of non-target lesions, which are not assessed at a particular timepoint based on the assessment schedule, should be excluded from the response determination (e.g. non-target response does not have to be "Not Evaluable").

New lesions

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

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

Evaluation of overall response

Table 11 presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for subjects with measurable disease at baseline.

Table 11 Evaluation of Overall Response for Subjects with Measurable Disease at Baseline

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

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

Note:

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

Evaluation of best overall response

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

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

Confirmation Criteria:

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

References

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12.8. Appendix 8: Liver Safety Required Actions and Follow up Assessments

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

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

Liver Chemistry Stopping Criteria – Liver Stopping Event **Subject <u>with</u> entry criteria ALT≤ 2.5 x ULN**	
ALT-absolute	ALT ≥5xULN
ALT Increase	ALT ≥3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥3xULN **and** bilirubin ≥2xULN (**>**35% direct bilirubin)
INR[2]	ALT ≥3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥3xULN **and** cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Liver Chemistry Stopping Criteria – Liver Stopping Event **Including subjects <u>with documented</u> liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN**	
ALT-absolute	**Both** ALT ≥5xULN **and** ≥2x baseline value
ALT Increase	**Both** ALT ≥3xULN **and** ≥1.5x baseline value that persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥3xULN **and** bilirubin ≥2xULN (**>**35% direct bilirubin)
INR[2]	ALT ≥3xULN **and** INR>1.5, if INR measured
Cannot Monitor	**Both** ALT ≥3xULN **and** ≥1.5x baseline value that cannot be monitored for 4 weeks
Symptomatic[3]	**Both** ALT ≥3xULN **and** ≥1.5x baseline value associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to Appendix 9) • If restart/rechallenge is **not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained approximately 48h after last dose[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications • Record alcohol use on the liver event alcohol intake case report form **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct high pressure liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥3xULN **and** bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN **and** INR>1.5, if INR

measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants

3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

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

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
Subject <u>with</u> entry criteria ALT≤2.5x ULN ALT ≥3xULN **but** <5xULN **and** bilirubin <2xULN, **without** symptoms believed to be related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks **Subject <u>with documented</u> liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN** ALT ≥3x ULN and 1.5x baseline value **but** ALT <5x ULN and 2x baseline value **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury, or hypersensitivity **and** who can be monitored weekly for 4 weeks	• Notify the Medical Monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline[1] • If at any time subject meets the liver chemistry stopping criteria, proceed as described above **For subjects with entry criteria ALT≤2.5 x ULN** • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline. **For subjects with documented liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN** • If, after 4 weeks of monitoring, ALT <3xULN and <1.5x baseline value, and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline

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

References

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

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

12.9. Appendix 9: Liver Safety – Study Treatment Restart or Rechallenge Guidelines

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

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

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

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

Risk factors for a fatal drug rechallenge outcome include:

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

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

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

- Investigator requests consideration of rechallenge with study treatment for a subject who is receiving compelling benefit with study treatment that exceeds risk, and no effective alternative therapy is available.
- Ethics Committee or Institutional Review Board approval for rechallenge with study treatment must be obtained, as required.

- If the rechallenge is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the rechallenge with study treatment. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for rechallenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If after study treatment rechallenge, subject meets protocol-defined liver chemistry stopping criteria, study treatment should be permanently discontinued.
- Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment rechallenge.
- GSK to be notified of any adverse events, as per Appendix 10.

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

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

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

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Restart risk factors (e.g. fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible study treatment-induced liver injury or study treatment has an HLA genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded
- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.
- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of

study treatment administration, including the possibility of recurrent, more severe liver injury or death.

- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment restart.
- GSK to be notified of any adverse events, as per Appendix 10.

References*:*

- Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-714.
- Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatol. 2010;52:2216-2222.
- Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, Hunt CM. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009;54:84-90.

12.10. Appendix 10: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.10.1. Definition of Adverse Events

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

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

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

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.10.2. Definition of Serious Adverse Events

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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

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

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea,

influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.
• Refer to Appendix 8 for the required liver chemistry follow-up instructions

12.10.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

12.10.4. Recording of AEs and SAEs

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

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

12.10.5. Evaluating AEs and SAEs

Assessment of Intensity

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

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

Assessment of Causality

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

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

Follow-up of AEs and SAEs

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

12.10.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

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

12.11. Appendix 11: Genetic Research

Genetics – Background

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

Genetic Research Objectives and Analyses

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

- Response to medicine, including GSK525762 and/or fulvestrant, or any concomitant medicines;
- Breast cancer susceptibility, severity, and progression and related conditions

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

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

Study Population

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

Study Assessments and Procedures

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

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

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

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

Subjects can request their sample to be destroyed at any time. With the implementation of amendment 06, if a subject has consented for genetic research but the sample has yet to be collected, this will no longer be required.

Informed Consent

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

Subject Withdrawal from Study

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

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

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

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

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

Screen and Baseline Failures

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

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

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

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

References

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

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

12.12. Appendix 12: Country Specific Requirements

The changes in amendment 02 apply to all sites in the United Kingdom.

12.13. Appendix 13: Child-Pugh score

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

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

Reference:

Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973 Aug;60(8):646-9.

12.14. Appendix 14: Protocol Amendment Changes

12.14.1. Amendment 01

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

Amendment 1 summary:

Amendment 1 applies to all global study sites.
Based upon review and comment on the protocol by the FDA, the following changes are being implemented: Clarification of the permitted prophylactic anticoagulation therapies in Exclusion Criteria #4; Correction of the spelling of goserelin throughout the protocol; Clarification of how to read the liver algorithms in Section 5.4.1; Changes to the toxicity management guidelines in Appendix 2, Table 12 for the following: Update to the dose interruption/ reduction/discontinuation guidelines for Grade 4 thrombocytopenia; Dose reduction for subjects if QTcF ≥ 60 msec change from baseline occurs OR QTcF ≥ 500; Permanent discontinuation of study medication for subjects with troponin levels approaching the threshold for MI; Clarification on length of follow-up for subjects with LVEF increase; Monitoring of blood sugar and dose reduction guidelines for subjects with moderate to severe hypoglycemia; Dose reduction and event management for subjects with Grade 3-4 diarrhea; Dose interruption and reduction for subjects with Grade 3-4 mucositis; Dose interruption/reduction/discontinuation and event management for all Grades of pneumonitis; Dose interruption and/or reduction for subjects with Grade 3-4 other non-hematologic events.
In addition to these requested changes from the FDA, other administrative changes to the protocol include: Clarification of timing for sites to report pregnancies to GSK (24 hours versus 2 weeks, based on reproductive toxicity seen in pre-clinical GSK525762 studies); Correction of spelling errors; Correction to the Medical Monitor contact information; Correction of a typo in the Phase 1 Time and Events table; Addition of clarifying language around survival follow up after the EoT visit; Addition of clarifying language around fresh biopsies; Addition of clarifying language around the timing of CBC draws in Week 1; Addition of clarifying language to inclusion criteria #6 and exclusion criterion #1-3 around prior treatment history; Clarified wording around disease assessment schedule after Week 52; Removal of Section 5.4.3.2 Valvular Toxicity Stopping Criteria, this section is part of the GSK template guidance and not mandatory for inclusion, and there are no pre-clinical/clinical valvular toxicity findings for GSK525762. Removal of this information will also reduce the number of assessments required for subjects; Update to the option of scan (now ECHO or MUGA) performed to monitor cardiac safety; Removal of Section 7.3.5.6 Disease Related Events, this section is only to be included if there are pre-defined disease related events, and this protocol has no pre-defined events; Update to the Grade 3 and Grade 4 thrombocytopenia management guidelines to make them more stringent, based upon emerging data that will be provided in an INDSR (October 2016); Removal of the fever management guidelines in Appendix 2, Table 12, as part of the ongoing safety review for GSK525762, there is no apparent clinical correlation to the preclinical in vitro findings suggesting a potential for fever.

List of Specific Changes

Medical Monitor/Sponsor Information Page

Rationale Change 1:

Corrected the contact information for Dr. PPD.

Previous text:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Site Address and email address
Primary Medical Monitor	PPD MD	PPD	PPD	GlaxoSmithKline 1250 South Collegeville Road, UP4410 Collegeville, PA 19426, USA PPD
Secondary Medical Monitor	PPD MD, PhD	PPD	PPD	GlaxoSmithKline 1250 South Collegeville Road, UP4410 Collegeville, PA 19426, USA PPD

Revised text:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Site Address and email address
Primary Medical Monitor	PPD MD	PPD	PPD	GlaxoSmithKline 1250 South Collegeville Road, UP4410 Collegeville, PA 19426, USA PPD
Secondary Medical Monitor	PPD MD, PhD	PPD	PPD	GlaxoSmithKline 1250 South Collegeville Road, UP4410 Collegeville, PA 19426, USA PPD

Medical Monitor/Sponsor Information Page

Rationale Change 2:

A separate IND has been opened for this study, therefore a new IND# has been generated and added to the protocol.

Previous text:

Regulatory Agency Identifying Number(s): Investigational New Drug (IND) # IND112942, EudraCT number 2016-003074-40

Revised text:

Regulatory Agency Identifying Number(s): Investigational New Drug (IND) # IND~~112942~~**131933**, EudraCT number 2016-003074-40

Synopsis Rationale / Section 2.1 Brief Background

Rationale Change 3:

Clarified wording around fulvestrant's mechanism of action.

Previous text:

Currently, approved endocrine therapies include the ER antagonist tamoxifen; the aromatase inhibitors (AIs) anastrozole, exemestane, and letrozole; and a selective ER degrader fulvestrant.

Revised text:

Currently, approved endocrine therapies include the ER antagonist tamoxifen; the aromatase inhibitors (AIs) anastrozole, exemestane, and letrozole; **and fulvestrant, a selective ER antogonist**.

Section 4.7.1.2.1 Risk Assessment, Predicted Single Agent Toxiticities, Cardiovascular Safety Findings, Management and Monitoring

Rationale for Change 4:

To accommodate local practice, both ECHO and MUGA scans can be used to monitor cardiac safety.

Previous text:

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

Revised text:

To monitor for cardiomyopathy and valvular toxicity, echocardiograms **or multigated acquisition (MUGA) scan** will be performed at the time points specified in the Time and Events tables (Section 7.1). Management guidelines (Appendix 2) and stopping criteria (Section 5.4.2 and Section 5.4.3) are incorporated in the protocol. **Please refer to the study reference manual (SRM) for further detail.**

This change is also applied to Section 5.1 (pg 46), Section 5.4.3 (pg 53), Section 7.1 (pg 66-69), Section 7.2.2 (pg71), Section 7.3.3.2 (pg73), Section 9.4.4.1 (pg 90), Appendix 1 (pg105)

Section 5.1 Inclusion Criteria – Inclusion #6

Rationale Change 5:

Clarification on prior treatment history for eligible subjects.

Previous text:

History of prior therapy that satisfies one of the following criteria:

d. Disease that progressed during treatment or within 12 months of completion of adjuvant therapy with tamoxifen and/or an AI
e. Disease that progressed during treatment or within 1 month after the end of treatment with prior tamoxifen, AI, or CDK4/6 inhibitor plus letrozole, for advanced/metastatic disease

Revised text:

History of prior therapy that satisfies one of the following criteria:

a. **AI failures:** Disease that progressed during treatment or within 12 months of completion of adjuvant therapy with tamoxifen and/or an AI
b. **CDK4/6 inhibitor plus letrozole fairlures:** Disease that progressed during treatment or within 1 month after the end of treatment with prior tamoxifen, AI, **or the combination of a** CDK4/6 inhibitor plus letrozole,for advanced/metastatic disease

Section 5.1 Inclusion Criteria – Inclusion #7

Rationale Change 6:

Correction of the spelling of goserelin.

Previous text:

16. Any menopausal status

    NOTE: If pre- or peri-menopausal at time of enrollment (refer to Section 6.10.2.1 for menopause definition), subject must be willing to initiate therapy or continue ongoing therapy with gosrelin for at least 28 days prior to the first dose of fulvestrant. Subjects on an alternative Luteinizing hormone-releasing hormone (LHRH) agent do

not have to start gosrelin prior to the first dose of fulvestrant, but they must agree to change to gosrelin at the next scheduled dose and remain on gosrelin for the remainder of the trial

Revised text:

17. Any menopausal status

    NOTE: If pre- or peri-menopausal at time of enrollment (refer to Section 6.10.2.1 for menopause definition), subject must be willing to initiate therapy or continue ongoing therapy with **goserelin** for at least 28 days prior to the first dose of fulvestrant. Subjects on an alternative Luteinizing hormone-releasing hormone (LHRH) agent do not have to start **goserelin** prior to the first dose of fulvestrant, but they must agree to change to **goserelin** at the next scheduled dose and remain on **goserelin** for the remainder of the trial

Section 5.2 Exclusion Criteria – Exclusion #1

Rationale Change 7:

Clarification of wording on prior treatment.

Previous text:

Prior therapy with more than one line of cytotoxic chemotherapy following diagnosis of advanced/metastatic disease, or disease which has progressed despite prior fulvestrant therapy.

Note: Prior cytotoxic therapy in the neoadjuvant/adjuvant setting does not count toward the one line limit

Revised text:

Prior therapy with more than one line of cytotoxic chemotherapy following diagnosis of advanced/metastatic disease~~, or disease which has progressed despite prior fulvestrant therapy~~.

Note: Prior cytotoxic therapy in the neoadjuvant/adjuvant setting does not count toward the one line limit

Section 5.2 Exclusion Criteria – Exclusion #2

Rationale Change 8:

Clarification of wording on prior treatment.

Previous text:

This is a new exclusion criterion.

Revised text:

Disease which has progressed despite prior fulvestrant therapy.

Section 5.2 Exclusion Criteria – Exclusion #3

Rationale Change 9:

Clarification of wording on prior treatment.

Previous text:

This is a new exclusion criterion.

Revised text:

≥3 lines of systemic anti-cancer therapy (including 1 line of chemotherapy).

Section 5.2 Exclusion Criteria – Exclusion # 6

Rationale Change 10:

Clarification of what specific prophylactic anticoagulation treatments are permitted.

Previous text:

Therapeutic-dose anticoagulation (e.g., warfarin, low-molecular weight heparin [LMWH], or novel oral anticoagulants) must be discontinued and coagulation parameters must be normalized prior to the first dose of GSK525762 and fulvestrant. Low dose (prophylactic) LMWH or noval oral anticoagulant therapy is permitted.

Revised text:

Therapeutic-dose anticoagulation (e.g., warfarin, low-molecular weight heparin [LMWH], or novel oral anticoagulants) must be discontinued and coagulation parameters must be normalized prior to the first dose of GSK525762 and fulvestrant. ~~Low dose (prophylactic) LMWH or noval oral anticoagulant therapy is permitted.~~ **Prophylactic anticoagulation, with low doses (per standard practice) of agents such as low molecular weight heparin (LMWH), direct thrombin inhibitors, or factor Xa inhibitors is permitted.**

Section 5.4.1 Liver Chemistry Stopping Criteria

Rationale Change 11:

Provided clarification of how to read the liver algorithms (Figure 4 and Figure 5).

Previous text:

See Figure 4 and Figure 5 for liver stopping criteria for subjects without and with liver metastases, respectively.

Revised text:

See Figure 4 and Figure 5 for liver stopping criteria for subjects without and with liver metastases, respectively. **The algorithms are best read from left to right**.

Section 5.4.3.2 Valvular Toxicity Stopping Criteria

Rationale for change 12:

Language in this section is protocol template text, and not specific or relevant to GSK525762.

Previous text:

Subjects who have a new asymptomatic, moderate regurgitation or stenosis by echocardiogram (ECHO) (Grade 2 mitral/tricuspid/aortic valvular toxicity per National Cancer Institute- Common Toxicity Criteria for Adverse Events [NCI-CTCAE], version 4) should temporarily discontinue GSK525762 and/or fulvestrant, and have a repeat evaluation by ECHO within 1 week. ECHO should be repeated every 1 to 2 weeks for 4 weeks or until valve recovery to baseline.

- If the valve recovers to baseline any time during the next 4 weeks after consultation and approval of the Medical Monitor, the subject may be restarted on GSK525762 and/or fulvestrant at a reduced dose(s). For such subjects, monitoring of the valve via ECHO will then be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 16 weeks and then per protocol.
- If repeat ECHO does not reveal valve recovery to baseline within 4 weeks, then the subject should permanently discontinue GSK525762 and/or fulvestrant. The valve should continue to be monitored via ECHO every 4 weeks for 16 weeks or until resolution.

Subjects with a Grade 3 or 4 (symptomatic, severe regurgitation/stenosis by imaging with symptoms controlled by medical intervention) valvular toxicity must discontinue GSK525762 and/or fulvestrant. Valvular toxicity should continue to be monitored every 4 weeks for 16 weeks or until resolution. If recovery occurs (return to baseline via imaging AND symptom resolution) within 4 weeks, the subject may restart GSK525762 and/or fulvestrant at a reduced dose after consultation and approval of the Medical Monitor.

ECHO must be performed at baseline and at the final study visit. Copies of all ECHO(s) and cardiology consultations performed on subjects who experience valvular toxicity will be required by GSK for review. Instructions for submitting qualifying ECHOs are provided in the SRM.

Revised text:

Section has been removed.

Section 5.4.4 Other Stopping Criteria

Rationale Change 13:

Clarification that CBCs drawn during Phase I, Week 1 will include screening.

Previous text:

To monitor for hematologic toxicity, CBCs will be drawn three times during the first week , twice weekly for the next two weeks of study, once during the fourth week, and then every four weeks, as described in the Time and Events table.

Revised text:

To monitor for hematologic toxicity, CBCs will be drawn three times during the first week **(includes screening),** twice weekly for the next two weeks of study, once during the fourth week, and then every four weeks, as described in the Time and Events table.

Section 7.1 Time and Events Tables – Table 5 and Table 7 Time and Events

Rationale Change 14:

A footnote has been added to the Time and Events tables for Phase I and Phase II to clarify survival follow-up post the EoT visit.

Previous text:

This is new text

Revised text:

Applies to subjects who withdraw for any reason prior to progression or who progress during study treatment. Following this visit, subjects will be contacted approximately every 3 months (± 14 days) to collect: survival status as of last date of contact and initiation of new anti-cancer therapy. Contact may be completed via a clinic visit, a telephone contact or an email.

Section 7.1 Time and Events Tables – Table 6 Time and Events, Phase I Laboratory Assessments

Rationale Change 15:

Correction of a typo in the visit schedule for Phase I, Week 3.

Previous text:

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

1. Only required at screening for pre- and peri-menopausal subjects

2. Serum pregnancy test within 7 days prior to first dose; urine or serum test thereafter

Revised text:

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

1. Only required at screening for pre- and peri-menopausal subjects

2. Serum pregnancy test within 7 days prior to first dose; urine or serum test thereafter

Section 7.1 Time and Events Tables – Table 5 Time and Events, Phase I Footnote 10

Rationale Change 16:

Addition of clarifying language around the fresh biopsies needed for the study.

Previous text:

Screening (archival) tumor biopsy specimen required for all subjects; if archival sample is not available then fresh specimen must be provided as described in Section 7.7.2. Paired fresh biopsies must be provided pre- and on-treatment at the time points indicated for at least 6 subjects at each dose level. A limited number of additional subjects may be requested to provide pre and on-treatment biopsies based on emerging data. Fresh biopsies should be paired with plasma samples for PK, collected as close as possible to biopsy (ideally within 1 h). Refer to the SRM for further details.

Revised text:

Screening (archival) tumor biopsy specimen required for all subjects; if archival sample is not available then fresh specimen must be provided as described in Section 7.7.2. Paired fresh biopsies must be provided pre- and on-treatment at the time points indicated for at least 6 subjects **(out of 35 planned for enrollment)** at each dose level. A limited number of additional subjects may be requested to provide pre and on-treatment biopsies based on emerging data. Fresh biopsies should be paired with plasma samples for PK, collected as close as possible to biopsy (ideally within 1 h). Refer to the SRM for further details.

Section 7.2.2 Visit Windows

Rationale for change 17:

Clarification on wording for the disease assessment schedule after Week 52.

Previous text:

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

Revised text:

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

Section 7.3.5.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

Rationale Change 18:

There are no pre-defined disease related events identified for this study, so the section has been removed.

Previous text:

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

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

NOTE: If either of the following conditions applies, then the event is not a disease-related event (DRE) and must be recorded and reported as an SAE:

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual subject, or
- The investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product

Revised text:

Section has been removed.

Section 7.3.6 Pregnancy

Rationale Change 19:

Due to the pre-clinical reproductive toxicity findings with GSK525762, the timeframe for reporting of pregnancies by sites to GSK has been changed from 2 weeks to 24 hours.

Previous text:

Details of all pregnancies in female participants will be collected after the start of study treatment and until at least 90 days post-last dose.

If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined Appendix 4.

Revised text:

Details of all pregnancies in female participants will be collected after the start of study treatment and until at least 90 days post-last dose.

If a pregnancy is reported then the investigator should inform GSK within **24 hours** of learning of the pregnancy and should follow the procedures outlined Appendix 4.

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

Section 7.5.1 Tumor Biopsy Collection

Rationale Change 20:

Addition of clarifying language around the fresh biopsies needed for the study.

Previous text:

In Phase I, paired fresh biopsies must be provided pre- (within 14 days of the first dose) and on-treatment at the time points indicated for at least 6 subjects at each dose level. A limited number of additional subjects may be requested to provide pre and on-treatment biopsies based on emerging data. Biopsy requirement(s) will be discussed with the subject prior to signing informed consent. Any fresh on-treatment biopsy should be accompanied by a plasma sample collected as close as possible to the time of biopsy (preferably within 1 h). Further details regarding sample type and processing will be provided in the SRM.

Revised Text:

In Phase I, paired fresh biopsies must be provided pre- (within 14 days of the first dose) and on-treatment at the time points indicated for at least 6 subjects **(out of 35 planned for enrollment)** at each dose level. A limited number of additional subjects may be requested to provide pre and on-treatment biopsies based on emerging data. Biopsy requirement(s) will be discussed with the subject prior to signing informed consent. Any fresh on-treatment biopsy should be accompanied by a plasma sample collected as close as possible to the time of biopsy (preferably within 1 h). Further details regarding sample type and processing will be provided in the SRM.

Section 12.2 Appendix 2: Management of Suspected Toxicity

Rationale Change 21:

Based upon newly available data (provided in a recent INDSR), the Grade 3 thrombocytopenia management guidelines have been updated to be more stringent.

Previous text:

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Thrombocytopenia	Grade 3 (platelets <50,000, ≥25,000/mm^3)	After discussion with medical monitor and using sound clinical judgement, continue GSK525762 at same dose or dose reduce to previously cleared dose level. Monitor CBC at least twice a week, or more frequently if clinically indicated. Investigators should delay fulvestrant injections until platelet count recovers to ≤ Grade 2 (>50,000/mm^3).

Revised text:

Toxicity	Dose Adjustment/ Stopping Criteria	**Management Guidelines**
Thrombocytopenia	Grade 3 (platelets <50,000, ≥25,000/mm^3)	Withhold GSK525762 and check aPTT, PT, and INR. Monitor CBC and coagulation studies at least twice a week, or more frequently if clinically indicated. Hold GSK525762 until thrombocytopenia has resolved to ≤ Grade 2 AND aPTT, PT, and INR are all ≤ ULN. Drug may then be restarted at the same dose or at lower dose level, after discussion with medical monitor. If safety lab abnormalities recur following rechallenge, drug may be discontinued or restarted at a lower dose level, after discussion with medical monitor. As per the fulvestrant package insert, because fulvestrant is administered intramuscularly, it should be used with caution in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use.

Section 12.2 Appendix 2: Management of Suspected Toxicity – Table 12: Dose Adjustment/Stopping Safety Criteria Grade 4 Thrombocytopenia

Rationale Change 22:

Based upon feedback from the FDA, and newly available data (provided in a recent INDSR), the management guidelines for Grade 4 thrombocytopenia have been updated to be more stringent.

Previous text:

Toxicity	**Dose Adjustment/ Stopping Criteria**	**Management Guidelines**
Thrombocytopenia	Grade 4 (platelets <25,000/mm3),and/or any grade accompanied by severe bleeding related to thrombocytopenia	Temporarily interrupt GSK525762 and monitor CBC every 2-3 days. If platelet counts recover to Grade 3 and is steady for at least 2 CBC reads at least 3days apart, or rising, discuss with medical monitor resuming treatment at the same or adjusted dose (see Grade 3) based on sound clinical judgment. Investigators should delay fulvestrant injections until platelet count recovers to ≤ Grade 2 (>50,000/mm^3).

Revised text:

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Thrombocytopenia	Grade 4 (platelets <25,000/mm3), or any moderate to severe bleeding accompanied by drug related thrombocytopenia	Withhold GSK525762 and check aPTT, PT, and INR. Monitor CBC and coagulation studies every 2-3 days. Hold GSK525762 until thrombocytopenia has resolved to ≤ Grade 2 AND aPTT, PT, and INR are all ≤ ULN. Drug may then be restarted at a lower dose level, after discussion with medical monitor. If safety lab abnormalities recur following rechallenge, drug may be discontinued until platelet count recovers to Grade 2 (≥50,000u/l). As per the fulvestrant package insert, because fulvestrant is administered intramuscularly, it should be used with caution in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use For subjects with moderate to severe bleeding requiring transfusion support, GSK525762 should be permanently discontinued. If platelet count does not recover to ≥50,000/ul (Grade 2) within 14 days, GSK525762 should be permanently discontinued. If platelet count recovers to ≥50,000/ul (Grade 2) within 14 days, GSK525762 may be continued at the current/reduced dose after discussion with the medical monitor .

Section 12.2 Appendix 2: Management of Suspected Toxicity – Table 12: Dose Adjustment/Stopping Safety Criteria QTcF

Rationale Change 23:

Based upon feedback from the FDA, the management guidelines for QTcF restart if ≥ 60 msec change from baseline occurs OR QTcF ≥500 have been updated to incorporate a dose reduction.

Previous text:

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
QTcF	If ≥ 60 msec change from baseline occurs OR QTcF ≥500 (average of three ECGs over at least 15 minutes)	Discontinue GSK525762 and notify the Medical Monitor. • Supplement electrolytes to recommended levels: c. Maintain serum potassium > 4mol/L d. Maintain serum magnesium levels >0.85 mmol/L • Rule out other potential etiologies for prolonged QTcF such as cardiac ischemia • Discontinue any concomitant medications with potential for QTcF prolongation. • Consider telemetry monitoring if clinically indicated. This subject may consider restarting study treatment at a previously cleared dose level if all of the following criteria for QTcF re-challenge are met. If approval for re-challenge is granted, the subject must be re-consented (with a separate informed consent specific to QTc prolongation) (6) QTcF reduced to <450 msec, (7) Potassium and magnesium levels are within institutional normal range, (8) A favorable risk/benefit profile (in the medical judgement of the Investigator and the Medical Monitor), (9) Approval within GSK medical governance: a. agreement with SERM MD and PPL, b. review with Chair or co-Chair of the GSK QT panel, c. SERM VP and Clinical VP approval d. Head Unit Physician approval (10) Institutional IRB (or equivalent) approval, and (11) The subject is re-consented regarding the possible increased risk of QTc prolongation. • Discontinuation procedures: If the subject is withdrawn due to QTcF event, the subject should complete the following activities post-dose: (4) Evaluation by cardiologist. (5) Weekly assessments for QTcF should be performed for two weeks, and then next assessment at 4 weeks post-dose. • If QTcF results have not resolved to baseline by 4 weeks post-dose, then continue every 4-5 weeks until resolution

Revised text:

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

Section 12.2 Appendix 2: Management of Suspected Toxicity – Table 12: Dose Adjustment/Stopping Safety Criteria Troponin Level Increase

Rationale Change 24:

Based upon feedback from the FDA, the management guidelines for elevated troponin levels have been updated.

Previous text:

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Troponin	Troponin level >ULN	Contact the subject immediately for evaluation of symptoms and to obtain ECG. Repeat troponin as soon as possible (ideally within 24-48 hours). For asymptomatic subjects with repeat troponin values >ULN, hold study medication(s), refer to a cardiologist and contact the Medical Monitor. If the repeat value is within the normal range, the subject may continue study medication with close follow-up for symptoms, ECG monitoring and further troponin measurements as clinically indicated. If the subject is symptomatic or the troponin level approaches the threshold for MI according to local lab parameters, the study medication must be withdrawn and the subject will be referred immediately to a cardiologist for appropriate medical care. May consider restarting study treatment at a reduced dose based on discussion with Medical Monitor.

Revised text:

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Troponin	Troponin level >ULN	Contact the subject immediately for evaluation of symptoms and to obtain ECG. Repeat troponin as soon as possible (ideally within 24-48 hours). For asymptomatic subjects with repeat troponin values >ULN, hold study medication(s), refer to a cardiologist and contact the Medical Monitor. If the repeat value is within the normal range, the subject may continue study medication with close follow-up for symptoms, ECG monitoring and further troponin measurements as clinically indicated. If the subject is symptomatic or the troponin level approaches the threshold for MI according to local lab parameters, the study medication must be ~~withdrawn~~

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
		permanently discontinued and the subject will be referred immediately to a cardiologist for appropriate medical care. ~~May consider restarting study treatment at a reduced dose based on discussion with Medical Monitor.~~

Section 12.2 Appendix 2: Management of Suspected Toxicity – Table 12: Dose Adjustment/Stopping Safety Criteria elevated LVEF

Ration Rationale Change 25:

Based upon feedback from the FDA, the management guidelines on length of follow up for elevated LVEF have been updated.

Previous text:

LVEF	• Asymptomatic, absolute decrease of >10% in LVEF compared to baseline and the ejection fraction is below the institution's lower limit of normal (LLN)	• Interrupt investigational drug(s) and repeat evaluation of LVEF within 2 weeks • If LVEF recovers (defined as ≥LLN and absolute decrease ≤10% compared to baseline) at any time during the next 4 weeks, after consultation and approval of the Medical Monitor, the subject may be restarted on investigational drug(s) at a reduced dose. Monitoring to be performed at 2 and 4 weeks after restarting investigational drug(s) and then per protocol specifications. • If LVEF does not recover within 4 weeks, permanently discontinue investigational drug(s). Evaluation by a cardiologist will be conducted. Ejection fraction should continue to be monitored at 2 weeks, 4 weeks and every 4 weeks until 16 weeks or resolution.
	• Grade 3 or 4	• Permanently discontinue investigational drug(s). Evaluation by a cardiologist will be conducted. Ejection fraction should be monitored at 2 weeks, 4 weeks and then every 4 weeks until 16 weeks or resolution.

Revised text:

LVEF	• Asymptomatic, absolute decrease of >10% in LVEF compared to baseline and the ejection fraction is below the institution's lower limit of normal (LLN)	• Interrupt investigational drug(s) and repeat evaluation of LVEF within 2 weeks • If LVEF recovers (defined as ≥LLN and absolute decrease ≤10% compared to baseline) at any time during the next 4 weeks, after consultation and approval of the Medical Monitor, the subject may be restarted on investigational drug(s) at a reduced dose. Monitoring to be performed at 2 and 4 weeks after restarting investigational drug(s) and then per protocol specifications. • If LVEF does not recover within 4 weeks, permanently discontinue investigational drug(s). Evaluation by a cardiologist will be conducted. Ejection fraction should continue to be monitored at 2 weeks, 4 weeks and every 4 weeks until 16 weeks or resolution **whichever is longer.**
	• Grade 3 or 4	• Permanently discontinue investigational drug(s). Evaluation by a cardiologist will be conducted. Ejection fraction should be monitored at 2 weeks, 4 weeks and then every 4 weeks until 16 weeks or resolution **whichever is longer.**

Section 12.2 Appendix 2: Management of Suspected Toxicity – Table 12: Dose Adjustment/Stopping Safety Criteria Moderate to Severe Hypoglycemia

Rationale Change 26:

Based upon feedback from the FDA, the management guidelines for moderate to severe hypoglycemia have been updated.

Previous text:

Toxicity	**Dose Adjustment/ Stopping Criteria**	**Management Guidelines**
Hypo- and Hyperglycemia (for management purposes, refer to mild, moderate and severe intensity criteria; however for CRF reporting use NCI-CTCAE v4.0 [NCI] grading system)	• Fasting blood glucose <70 mg/dL (Moderate to Severe hypoglycemia)	• Hold investigational product(s) • Provide sugar containing liquids and monitor blood sugar closely. Check for insulin and c-peptide levels. After blood sugar normalizes • May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with Medical Monitor

Revised text:

Toxicity	**Dose Adjustment/ Stopping Criteria**	**Management Guidelines**
Hypo- and Hyperglycemia (for management purposes, refer to mild, moderate and severe intensity criteria; however for CRF reporting use NCI-CTCAE v4.0 [NCI] grading system)	• Fasting blood glucose <70 mg/dL (Moderate to Severe hypoglycemia)	• Hold investigational product(s) • Provide sugar containing liquids and monitor blood sugar closely. Check for insulin and c-peptide levels. After blood sugar normalizes • ~~May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with Medical Monitor~~ • **Restart study treatment one dose level lower if the hypoglycemia cannot be attributed to any other cause, and fasting blood sugar will be monitored on a daily basis until the blood glucose level is stabilized.**

Section 12.2 Appendix 2: Management of Suspected Toxicity – Table 12: Dose Adjustment/Stopping Safety Criteria Grade 3-4 Diarrhea

Rationale Change 27:

Based upon feedback from the FDA, the management guidelines for Grade 3-4 diarrhea have been updated.

Previous text:

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Diarrhea	• Grade 3 or 4	• Above plus consider IV hydration, hospital admission and prophylactic antibiotics as appropriate. Consider temporary discontinuation of study medications and discuss with Medical Monitor. • May restart study treatment at a reduced dose or dose level pre-event based on discussion with Medical Monitor.

Revised text:

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Diarrhea	• Grade 3 or 4	• Above plus consider IV hydration, hospital admission and prophylactic antibiotics as appropriate. ~~Consider temporary discontinuation of study medications and discuss with Medical Monitor.~~ **Withhold study drug until diarrhea has resolved to ≤Grade 1, continue diarrheal prophylaxis** • ~~May restart study treatment at a reduced dose or dose level pre-event based on discussion with Medical Monitor.~~ • **Restart study treatment one dose level lower**

Section 12.2 Appendix 2: Management of Suspected Toxicity – Table 12: Dose Adjustment/Stopping Safety Criteria Grade 3-4 Mucositis

Rationale Change 28:

Based upon feedback from the FDA, the management guidelines for Grade 3-4 mucositis have been updated.

Previous text:

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Mucositis	• Grade 3 or 4	• (Above plus systemic opiate administration as needed.) Consider IV hydration and hospital admission as appropriate. • May restart study treatment at a reduced dose or dose level pre-event based on discussion with Medical Monitor.

Revised text:

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Mucositis	• Grade 3 or 4	• (Above plus systemic opiate administration as needed.) Consider IV hydration and hospital admission as appropriate. • ~~May restart study treatment at a reduced dose or dose level pre-event based on discussion with Medical Monitor.~~ • For mucositis ≥ Grade 3, hold GSK525762 until mucositis is **≤ Grade 1** and resume the same dose of GSK525762. If **mucositis** ≥ Grade 3 recurs, hold GSK525762 until mucositis is **≤ Grade 1**, then reduce GSK525762 one dose level. If mucositis ≥ Grade 3 recurs a third time at reduced dose, hold GSK525762 until mucositis resolved to ≤ Grade 1, then reduce GSK525762 one dose level (if possible) or discontinue permanently.

Section 12.2 Appendix 2: Management of Suspected Toxicity – Table 12: Dose Adjustment/Stopping Safety Criteria Pneumonitis

Rationale Change 29:

Based upon feedback from the FDA, the management guidelines for pneumonitis have been updated.

Previous text:

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Pneumonitis	• Grade 1	• (For <u>all</u> Grades) Obtain high resolution chest CT. • Consider evaluation by pulmonologist. Consider room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). Repeat evaluations every 8-12 weeks until return to within normal limits (wnl). • Continue investigational drug(s) at current dose(s).
	• Grade 2	• Hold investigational drug(s) until recovery to ≤ Grade 1, then reduce dose by at least 25%. Discontinue investigational drug(s) if no recovery to ≤ Grade 1 within 4 weeks. May consider escalation to pre-event dose after discussion with Medical Monitor. • Consider evaluation by pulmonologist. Consider pulmonary function tests including: spirometry, Diffusing Capacity of the Lung for Carbon Monoxide (DLCO), and room air O2 saturation at rest via pulse

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
		oximetry reading (X 2, 5 mins apart). Repeat evaluations every 8-12 weeks until return to wnl. Consider a bronchoscopy with biopsy and/or bronchoalveolar lavage. (BAL). • Treat only if symptomatic. Consider corticosteroids if symptoms are troublesome and infectious origin is ruled out. Taper as medically indicated.
	• Grade 3 and 4	• (Grade 3) Hold investigational drug(s) until recovery to ≤ Grade 1; may consider restarting investigational drug(s) at a reduced dose(s) after discussion with Medical Monitor. Discontinue investigational drug(s) if no recovery to ≤ Grade 1 within 4 weeks. (Grade 4) Discontinue investigational drug(s) • Evaluation by pulmonologist required. • Required pulmonary function tests including: spirometry, DLCO, and room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). Repeat evaluations at least every 8 weeks until return to normal. Bronchoscopy with biopsy and/or BAL is recommended. • Consider treatment with corticosteroids (1-2 mg/kg of prednisone [or equivalent] IV once daily) if infectious origin is ruled out. Taper over 4-6 weeks.

Revised text:

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Pneumonitis	• Grade 1	• (For <u>all</u> Grades) Obtain high resolution chest CT. • Consider evaluation by pulmonologist. Consider room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). ~~Repeat evaluations every 8-12 weeks until return to within normal limits (wnl).~~ • **If any decline is observed in O_2 saturation, hold study drug, repeat chest x-ray to determine if progression of pneumonitis has occurred and consult pulmonologist**. • ~~Continue investigational drug(s) at current dose(s).~~
	• Grade 2	• Hold investigational drug(s) until recovery to ≤ Grade 1, then reduce dose by at least 25%. Discontinue investigational drug(s) if no recovery to ≤ Grade 1 within 4 weeks. ~~May consider escalation to pre-event dose after discussion with Medical Monitor.~~ • ~~Consider evaluation~~ Must be evaluated by a pulmonologist. ~~Consider~~ Perform pulmonary function

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
		tests including: spirometry, Diffusing Capacity of the Lung for Carbon Monoxide (DLCO), and weekly room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). Repeat evaluations every 4 weeks until pneumonitis has resolved~~. 8-12 weeks until return to wnl~~. Consider a bronchoscopy with biopsy and/or bronchoalveolar lavage. (BAL). • Treat only if symptomatic. Consider corticosteroids if symptoms are troublesome and infectious origin is ruled out. Taper as medically indicated.
	• Grade 3 and 4	• (~~Grade 3) Hold investigational drug(s) until recovery to ≤ Grade 1; may consider restarting investigational drug(s) at a reduced dose(s) after discussion with Medical Monitor. Discontinue investigational drug(s) if no recovery to ≤ Grade 1 within 4 weeks. (Grade 4)~~ Discontinue investigational drug(s) • Evaluation by pulmonologist required. • Required pulmonary function tests including: spirometry, DLCO, and weekly room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). Repeat evaluations at least every 8 weeks until return to normal. Bronchoscopy with biopsy and/or BAL is recommended. • Consider treatment with corticosteroids **in the appropriate clinical setting and in consultation with the pulmonologist** (1-2 mg/kg of prednisone [or equivalent] IV once daily) if infectious origin is ruled out. Taper over 4-6 weeks.

Section 12.2 Appendix 2: Management of Suspected Toxicity – Table 12: Dose Adjustment/Stopping Safety Criteria Fever Management

Rationale Change 30:

Fever management guidelines have been removed due to lack of fever events seen in the ongoing BET115521 and BET116183 studies.

Previous text:

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Fever [b]	• Grade 1	• Continue current dose(s) of study treatment(s) and monitor for change in severity.
	• Grade 2	• Consider temporary discontinuation of study medication and monitor for change in severity. • Assess or inquire if the subject is experiencing in combination with fever: swelling, redness, extreme fatigue or nausea. Assess vital signs. • Collect "Cytokine blood samples" (which include blood sample for tumor Necrosis Factor (TNF)-alpha, Interleukin (IL)-1,IL-6, IL-10). Collect blood culture and investigate viral infections as applicable. • May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with Medical Monitor
	• Grade 3-4	• Temporary discontinuation of study medication and monitor for change in severity • Assess or inquire if the subject is experiencing in combination with fever: swelling, redness, extreme fatigue or nausea. • Collect "Cytokine blood samples" (which include blood sample for TNF-alpha, IL-1,IL-6, IL-10). Collect blood culture and investigate viral infections as applicable. • May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with Medical Monitor.

Revised text:

Section has been removed.

Section 12.2 Appendix 2: Management of Suspected Toxicity – Table 12: Dose Adjustment/Stopping Safety Criteria Grade 3-4 Other Non-Hematologic Events

Rationale Change 31:

Based upon feedback from the FDA, the management guidelines for Grade 3-4 other non-hematologic events have been updated.

Previous text:

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Other non-hematologic	• Grade 3	• Hold dose for one week intervals until ≤ drug-related Grade 2 then restart with no change for 1st episode.

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
toxicity (except those listed in Section 4.2.3.5)		Utilize an alternative, less frequent schedule or reduce by one dose level with 2nd episode. If no recovery to ≤Grade 1 after a 21 day delay, subject should go off protocol therapy.
	• Grade 4	• Off protocol therapy • In rare situations, based on discussion and written agreement between Medical Monitor and investigator, if the subject is receiving benefit then the following criteria should be implemented: hold dose for one week intervals until < drug-related Grade 2 then restart with no change for 1st episode. Utilize an alternative, less frequent schedule or reduce by one dose level with 2nd episode. If no recovery to ≤Grade 1* after a 21 day delay, subject should go off protocol therapy

Revised text:

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Other non-hematologic toxicity (except those listed in Section 4.2.3.5)	• Grade 3	• Hold dose ~~for one week intervals until ≤ drug-related Grade 2~~ until toxicity is ≤Grade 1, then restart with no change for 1st episode. ~~Utilize an alternative, less frequent schedule or~~ Reduce by one dose level with 2nd episode **if recovery to ≤Grade 1 within 21 days**. If no recovery to ≤Grade 1 after a 21 day delay in the 2nd episode, subject should be permanently discontinued ~~go off protocol therapy~~.
	• Grade 4	~~• Off protocol therapy~~ • ~~In rare situations, based on discussion and written agreement between Medical Monitor and investigator, if the subject is receiving benefit then the following criteria should be implemented: hold dose for one week intervals until < drug-related Grade 2 then restart with no change for 1st episode. Utilize an alternative, less frequent schedule or reduce by one dose level with 2nd episode. If no recovery to ≤Grade 1* after a 21 day delay, subject should go off protocol therapy~~ • In patients with objective evidence of clinical benefit, hold therapy until toxicity is ≤Grade 1, then restart with one dose level lower. If the same Grade 4 non-hematological toxicity recurs, study drug will be permanently discontinued.

12.14.2. Amendment 02

Protocol changes for Amendment 02, from protocol changes to amendment 01 (21-OCT-2016)

Amendment 02 summary:

Amendment 02 applies to all sites in the United Kingdom.
Based upon review and comment on the protocol by the MHRA, the following changes are being implemented as a standalone amendment for the UK: Clarification of the length of time, post treatment completion, that the approved list of contraceptives must be used by female subjects of childbearing potential; clarification in Section 5.4 that pregnancy is a reason for subject discontinuation from the study. A forthcoming amendment (03) will include these revisions as part of a global protocol amendment.

List of Specific Changes

Section 5.4 Withdrawal/Stopping Criteria

Rationale Change 1:

Clarification in this section that pregnancy of a subject taking part in the study is reason for discontinuation from study.

Previous text:

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

- deviation(s) from the protocol
- request of the subject or proxy (withdrawal of consent by subject or proxy)
- investigator's discretion
- subject is lost to follow-up
- study is closed or terminated
- a dose delay of >14 days unless the investigator and Medical Monitor agree that further treatment may benefit the subject

Revised text:

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

- deviation(s) from the protocol
- request of the subject or proxy (withdrawal of consent by subject or proxy)
- investigator's discretion
- subject is lost to follow-up
- study is closed or terminated

- a dose delay of >14 days unless the investigator and Medical Monitor agree that further treatment may benefit the subject
- **pregnancy**

Section 12.4 Appendix 4, Section 12.4.1 - Modified List of HighlyEffective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

Rationale Change 2:

Clarification of the length of time, post treatment completion, that the approved list of contraceptives must be used by female subjects of childbearing potential.

Previous text:

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

1. Intrauterine device (IUD) or intrauterine system
2. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

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

Revised text:

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

1. Intrauterine device (IUD) or intrauterine system
2. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

Note: Hormonal methods of contraception are not permitted since the efficacy of these methods in combination with GSK525762 has not been assessed. Hormone-releasing IUDs are a permitted form of contraception. LHRH-acting agents alone are not considered an adequate form of contraception. **GSK525762 has been shown to effect female reproductive systems in animals, therefore women of childbearing potential should adhere to this contraceptive guidance whilst on study and for 7 months after cessation of treatment with GSK525762.**

12.14.3. Amendment 03

Protocol changes for Amendment 03, from protocol changes to amendment 02 (31-JAN-2017

Amendment 03 summary:

Amendment 03 applies to all global study sites.

Changes to the protocol include: Clarification to the prior treatment subjects may have received; update to the timelines of the study, based upon new enrollment projections; clarification of inclusion criteria #6 regarding prior treatment subjects may have received; clarification of exclusion criteria #1 and #3 regarding number of prior lines of therapy; addition of two new exclusion criteria regarding use of NSAIDS and history of bleeding events; clarification in Section 5.4 that pregnancy for subjects of childbearing potential is a cause for study discontinuation; clarification regarding the liquid that subjects are permitted to use when taking GSK525762; clarification around the dosing window for fulvestrant; addition of Table 3 which clarifies dose reductions; clarification around use of Aspirin; update to the prohibited meds table in Section 6.11.2.1 and the cautionary meds table in Section 6.11.2.3; clarification around use of medication containing acetaminophen; update to the schedule of assessments in the Time and Events tables for both Phase I and II of the study; update to the schedule of laboratory assessments in both Phase I and II of the study; update to the ± visit windows for Weeks 2, 3, 4, 5, and 9; added logistical and medical guidance around when on treatment fresh biopsies and planned surgical procedure can take place; updated the thrombocytopenia management guidelines in Table 13 to be in line with regulatory feedback; clarification of baseline imaging windows; clarification of approved contraception and length of time said contraception needs to be used post study treatment.

List of Specific Changes

Title Page

Update to protocol author list

Previous text:

PPD [redacted]

Revised text:

PPD [redacted]

Section 1 Protocol Synopsis for Study 201973: Overall Design

Clarification of the design of Ph I

Previous text:

Phase I of the study is designed as single arm treatment with GSK525762 in combination with fulvestrant in two distinct populations of ER+ breast cancer to determine a recommended Phase 2 dose (RP2D) based on safety, tolerability, pharmacokinetic, and efficacy profiles.

Revised text:

Phase I of the study is designed as **parallel** single arm treatment with GSK525762 in combination with fulvestrant in two distinct populations of ER+ breast cancer to determine a recommended Phase 2 dose (RP2D) based on safety, tolerability, pharmacokinetic, and efficacy profiles.

Section 1 Protocol Synopsis for Study 201973: Overall Design

Clarification of the wording around the target subject population and prior therapy.

Previous text:

- Subjects who have disease that has progressed with an anti-estrogen and/or AI (e.g., tamoxifen, anastrozole, exemestane, and/or letrozole) plus up to one line of cytotoxic chemotherapy administered in the advanced/metastatic setting. Subjects receiving adjuvant tamoxifen or AI at the time of metastatic diagnosis, or subjects whose disease progressed within 12 months of discontinuing adjuvant tamoxifen or AI, will be eligible to enroll in this cohort.
- Subjects who have disease that has progressed during with a CDK4/6 inhibitor (e.g., palbociclib) plus letrozole (plus up to one line of cytotoxic chemotherapy administered in the advanced/metastatic setting and any number of lines of prior anti-estrogen and/or AI therapy)

Revised text:

- Subjects who have disease that has **relapsed during treatment or within 12 months of completion of adjuvant therapy with an AI, OR disease that progressed during treatment with an AI for advanced/metastatic disease. Prior ovarian suppression and/or tamoxifen are allowed as long as the other criteria are met.** ~~progressed with an anti-estrogen and/or AI (e.g., tamoxifen, anastrozole, exemestane, and/or letrozole) plus up to one line of cytotoxic chemotherapy administered in the advanced/metastatic setting. Subjects receiving adjuvant tamoxifen or AI at the time of metastatic diagnosis, or subjects whose disease progressed within 12 months of discontinuing adjuvant tamoxifen or AI, will be eligible to enroll in this cohort.~~
- Subjects who have disease that has progressed during **treatment** with **the combination of** a CDK4/6 inhibitor (e.g., palbociclib) plus letrozole **for advanced or metastatic disease. Prior ovarian suppression and/or tamoxifen are allowed as long as the other criteria are met.** ~~(plus up to one line of cytotoxic chemotherapy administered in the advanced/metastatic setting and any number of lines of prior anti-estrogen and/or AI therapy)~~

Documented progression on the last line of systemic anti-cancer therapy is required.

Section 2.2 Brief Background

To provide an update on the ER+BC cohort in the ongoing BET115521 monotherapy trial.

Previous text:

One inhibitor, GSK525762, is currently being studied in two separate trials: BET115521 and BET116183. Both are Phase I/II studies, with the primary endpoint to evaluate safety and tolerability of GSK525762 and identify the single-agent maximally-tolerated dose (MTD).

Revised text:

~~One inhibitor,~~ GSK525762, is currently being studied in two separate trials: BET115521 and BET116183. Both are Phase I/II studies, with the primary endpoint to evaluate safety and tolerability of GSK525762 and identify the single-agent maximally-tolerated dose (MTD). **In the ongoing BET115521 monotherapy trial, ER+ breast cancer subjects with disease that progressed after multiple prior lines of therapy were enrolled. A planned interim futility analysis in this population was performed, and GSK has stopped enrollment in this single agent cohort, based upon limited benefit.**

Section 4.1 Overall Design

Clarification of the design of Ph I

Previous text:

Phase I of the study is designed as single arm treatment with GSK525762 in combination with fulvestrant in two distinct populations of ER+ breast cancer to determine a recommended Phase 2 dose (RP2D) based on safety, tolerability, pharmacokinetic, and efficacy profiles.

Revised text:

Phase I of the study is designed as **parallel** single arm treatment with GSK525762 in combination with fulvestrant in two distinct populations of ER+ breast cancer to determine a recommended Phase 2 dose (RP2D) based on safety, tolerability, pharmacokinetic, and efficacy profiles.

Section 4.1 Overall Design: Phase I

Clarification of the wording around the target subject population and prior therapy.

Previous text:

Phase I will study the safety, tolerability, PK, and efficacy of GSK525762 plus fulvestrant when administered in combination in up to two escalating dose levels (DLs). Eligible subjects must have advanced or metastatic ER+BC that has been refractory to, or progressed despite, prior systemic therapy. The combination of GSK525762 plus fulvestrant will be evaluated in an open-label fashion in two separate populations of subjects (i.e., two cohorts). The same cohorts will be evaluated at multiple DLs:

- Subjects who have disease that has progressed on prior treatment with an anti-estrogen and/or AI (e.g., tamoxifen, anastrozole, exemestane, and/or letrozole) plus up to one line of cytotoxic chemotherapy administered in the advanced/metastatic setting
- Subjects who have disease that has progressed on prior treatment with a CDK4/6 inhibitor (e.g., palbociclib) plus letrozole (plus up to one line of cytotoxic chemotherapy administered in the advanced/metastatic setting and any number of lines of prior anti-estrogen and/or AI therapy)

Revised text:

Phase I will study the safety, tolerability, PK, and efficacy of GSK525762 plus fulvestrant when administered in combination in up to two escalating dose levels (DLs). Eligible subjects must have advanced or metastatic ER+BC that has been refractory to, or progressed despite, prior systemic therapy. The combination of GSK525762 plus fulvestrant will be evaluated in an open-label fashion in two separate populations of subjects (i.e., two cohorts). **These** ~~The same~~ cohorts will be evaluated at ~~multiple~~ **both** DLs **(see Inclusion and Exclusion criteria in Section 5.1 and Section 5.2 for full details):**

- Subjects who have disease that has **relapsed during treatment or within 12 months of completion of adjuvant therapy with an AI, OR disease that progressed during treatment with an AI for advanced/metastatic disease. Prior ovarian suppression and/or tamoxifen are allowed as long as the other criteria are met.** ~~progressed on prior treatment with an anti-estrogen and/or AI (e.g., tamoxifen, anastrozole, exemestane, and/or letrozole) plus up to one line of cytotoxic chemotherapy administered in the advanced/metastatic setting~~
- Subjects who have disease that has progressed during **treatment** with **the combination of** a CDK4/6 inhibitor (e.g., palbociclib) plus letrozole **for advanced or metastatic disease. Prior ovarian suppression and/or tamoxifen are allowed as long as the other criteria are met.** ~~(plus up to one line of cytotoxic chemotherapy administered in the advanced/metastatic setting and any number of lines of prior anti-estrogen and/or AI therapy)~~

Documented progression on the last line of systemic anti-cancer therapy is required.

Section 4.3.2 Phase II Cohort Selection

Clarification of the wording around the target subject population and prior therapy.

Previous text:

- either AI therapy OR CDK4/6 inhibitor plus letrozole. If both cohorts are permitted to enroll in Phase II, randomization will be stratified by prior CDK4/6 inhibitor-based therapy (i.e., CDK4/6 inhibitor-naïve versus CDK4/6 inhibitor-exposed) and corresponding stratified analysis will be provided at interim and final analyses

Note that in all cohorts, subjects may have received up to one line of cytotoxic chemotherapy in the advanced/metastatic setting. In addition, subjects enrolled in the CDK4/6 inhibitor plus letrozole and the CDK4/6 inhibitor plus fulvestrant cohorts may have failed therapy with any number of lines of anti-estrogens and/or AIs.

Revised text:

- either AI therapy OR CDK4/6 inhibitor plus letrozole. If both cohorts are permitted to enroll in Phase II, randomization will be stratified by prior CDK4/6 inhibitor-based therapy (i.e., CDK4/6 inhibitor-naïve versus CDK4/6 inhibitor-exposed) and corresponding stratified analysis will be provided at interim and final analyses

~~Note that in all cohorts, subjects may have received up to one line of cytotoxic chemotherapy in the advanced/metastatic setting. In addition, subjects enrolled in the CDK4/6 inhibitor plus letrozole and the CDK4/6 inhibitor plus fulvestrant cohorts may have failed therapy with any number of lines of anti-estrogens and/or AIs.~~

Section 4.6.2 Drug-Drug Interactions

Update wording around CYP3A4 induction of GSK525762.

Previous text:

Drugs as perpetrator: GSK525762 did not activate the human Pregnane X receptor (hPXR) in an in vitro assay (EC50 >50 μM). Based on *in vitro* studies, fulvestrant is not an inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. Co-administration of fulvestrant with midazolam, a sensitive substrate of CYP3A4, did not demonstrate any effect of fulvestrant administration on CYP3A4 activity.

Revised text:

GSK525762 did not activate the human Pregnane X receptor (hPXR) in an in vitro assay (EC50 >50 μM)**; although based on in vitro hepatocyte and repeat dose clinical pharmacokinetic data, GSK525762 has the potential to induce CYP3A4.**

Based on *in vitro* studies, fulvestrant is not an inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. Co-administration of fulvestrant with midazolam, a sensitive substrate of CYP3A4, did not demonstrate any effect of fulvestrant administration on CYP3A4 activity.

Section 4.7.1.1.1 Gastrointestinal Safety Findings

Referral to the full IB

Previous text:

GSK525762: No Grade 4 gastrointestinal effects were observed.

Revised text:

No Grade 4 gastrointestinal effects were observed. **Refer to the GSK525762 IB for full details.**

Section 4.7.1.1.3. Hematopoietic Safety Findings

Referral to the full IB

Previous text:

GSK525762: Thrombocytopenia was only noted after more than a week of continuous dosing, and platelet counts recovered after cessation of the drug.

Revised text:

Thrombocytopenia was only noted after more than a week of continuous dosing, and platelet counts recovered after cessation of the drug. **Refer to the GSK525762 IB for full details.**

Section 4.7.1.1.4. Reproductive Safety Findings

Referral to the full IB

Previous text:

GSK525762: Similarly, there have been no reports of pregnancy resulting from males on study with female partners of childbearing potential.

Revised text:

Similarly, there have been no reports of pregnancy resulting from males on study with female partners of childbearing potential. **Refer to the GSK525762 IB for full details.**

Section 4.7.1.2.1. Cardiovascular Safety Findings

Referral to the full IB

Previous text:

GSK525762: Full analysis of cardiac safety data will be performed at the end of dose escalation in the BET115521 study.

Revised text:

Full analysis of cardiac safety data will be performed at the end of dose escalation in the BET115521 study. **Refer to the GSK525762 IB for full details.**

Section 4.7.1.2.1. Cardiovascular Safety Findings

Removal of valvular toxicity wording that was erroneously left in post amendment 02.

Previous text:

Monitoring and Management: To monitor for cardiomyopathy and valvular toxicity, echocardiograms or multigated acquisition (MUGA) scan will be performed at the time points specified in the Time and Events tables (Section 7.1).

Revised text:

Monitoring and Management: To monitor for cardiomyopathy ~~and valvular toxicity~~, echocardiograms or multigated acquisition (MUGA) scan will be performed at the time points specified in the Time and Events tables (Section 7.1).

Section 5.1. Inclusion Criteria

Clarification of the wording around the target subject population and prior therapy.

Previous text:

6. History of prior therapy that satisfies one of the following criteria:
    a. AI failures: Disease that progressed during treatment or within 12 months of completion of adjuvant therapy with tamoxifen and/or an AI
    b. CDK4/6 inhibitor plus letrozole failures: Disease that progressed during treatment or within 1 month after the end of treatment with prior tamoxifen, AI, or the combination of a CDK4/6 inhibitor plus letrozole, for advanced/metastatic disease
7. Any menopausal status

Revised text:

6. History of prior therapy that satisfies one of the following criteria:
    a. AI failures: Disease that ~~progressed~~ **relapsed** during treatment or within 12 months of completion of adjuvant therapy with ~~tamoxifen and/or~~ an AI**, OR disease that progressed during treatment with an AI for advanced/metastatic disease. Prior ovarian suppression and/or tamoxifen are allowed as long as other criteria are met.**
    b. CDK4/6 inhibitor plus letrozole failures: Disease that progressed during treatment ~~or within 1 month after the end of treatment with prior tamoxifen, AI, or~~**with** the combination of a CDK4/6 inhibitor plus letrozole, for advanced/metastatic disease. **Prior ovarian suppression and/or tamoxifen are allowed as long as other criteria are met.**
7. **Documented progression on last line of systemic anti-cancer therapy is required.**
8. Any menopausal status

Section 5.1. Inclusion Criteria

Clarification of the length of time approved methods of contraception need to be used.

Previous text:

13. A female subject is eligible to participate if she is of:

- Non-childbearing potential defined in Section 6.10.2.1
- Child-bearing potential as defined in Section 6.10.2.2, and agrees to use one of the contraception methods as described in Appendix 4

Revised text:

14. A female subject is eligible to participate if she is of:

- Non-childbearing potential defined in Section 6.10.2.1
- Child-bearing potential as defined in Section 6.10.2.2, and agrees to use one of the contraception methods as described in Appendix 4**, from the time of the screening pregnancy test until 7 months after the last dose of study medication.**

Section 5.2. Exclusion Criteria

Clarification of the wording around the target subject population and prior therapy.

Previous text:

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

1. Prior therapy with more than one line of cytotoxic chemotherapy following diagnosis of advanced/metastatic disease.

   Note: Prior cytotoxic therapy in the neoadjuvant/adjuvant setting does not count toward the one line limit

2. Disease which has progressed despite prior fulvestrant therapy.
3. ≥3 lines of systemic anti-cancer therapy (including 1 line of chemotherapy).
4. Recent prior therapy, defined as:
   a. Any investigational or approved non-biologic anti-cancer drug within 14 days prior to the first dose of GSK525762 and fulvestrant.
   b. Any nitrosoureas or mitomycin C within 42 days prior to the first dose of GSK525762 and fulvestrant
   c. Any anti-cancer biologic agents within 28 days prior to the first dose of GSK525762 and fulvestrant
   d. Any radiotherapy within 30 days prior to the first dose of GSK525762 and fulvestrant. If the subject received radiotherapy <90 days prior to study treatment, the irradiated lesion cannot be the only lesion used for evaluating response.
   e. Any major surgery within 28 days prior to the first dose of GSK525762 and fulvestrant
5. Concomitant active malignancy other than ER+BC

NOTE: Subjects who have been disease-free and off therapy for 2 years, or subjects with a history of completely resected non-melanoma skin cancer or successfully treated *in situ* carcinoma are eligible.

Revised text:

1. **Prior therapy with any BET inhibitor, any selective estrogen receptor degrader (SERD) including fulvestrant, or inhibitors of the PI3K/AKT/mTOR pathway.**
2. Prior therapy with more than one line of cytotoxic chemotherapy following diagnosis of advanced/metastatic disease.

   ~~**Note**: Prior cytotoxic therapy in the neoadjuvant/adjuvant setting does not count toward the one line limit~~

~~3. Disease which has progressed despite prior fulvestrant therapy.~~

4. ≥3 lines of systemic anti-cancer therapy ~~(including 1 line of chemotherapy)~~ **in the advanced or metastatic setting.**

   NOTE:

   a. Prior systemic anti cancer therapy (cytotoxic chemo, hormonal, CD4/6K inhibitor therapies) in the neoadjuvant/adjuvant setting does not count toward the lines of therapy.

5. Recent prior therapy, defined as:

   a. Any investigational or approved non-biologic anti-cancer drug within 14 days **or five half-life (whichever is greater)** prior to the first dose of GSK525762 and fulvestrant.
   b. Any nitrosoureas or mitomycin C within 42 days prior to the first dose of GSK525762 and fulvestrant
   c. Any anti-cancer biologic agents within ~~28~~ **42** days prior to the first dose of GSK525762 and fulvestrant
   d. Any radiotherapy within 30 days prior to the first dose of GSK525762 and fulvestrant. If the subject received radiotherapy <90 days prior to study treatment, the irradiated lesion cannot be the only lesion used for evaluating response.
   e. Any major surgery within 28 days prior to the first dose of GSK525762 and fulvestrant

6. Concomitant active malignancy other than ER+BC

NOTE: Subjects who have been disease-free and off therapy for 2 years, or subjects with a history of **treated early stage cancers such as** completely resected non-melanoma skin cancer or successfully treated *in situ* carcinoma **of the cervix** are eligible. **Subjects with second malignancies that are indolent or definitively treated may be enrolled even if less than 2~~5~~ years have elapsed since treatment. Consult Medical Monitor if unsure whether second malignancies meet requirements specified above**

Section 5.2. Exclusion Criteria

Clarification around cardiac abnormality exclusion criteria.

Previous text:

11. Cardiac abnormalities as evidenced by any of the following:

- Baseline QTcF interval ≥450 msec
- Clinically significant conduction abnormalities or arrhythmia
- NOTE: Any clinically significant ECG assessments should be reviewed by the site cardiologist prior to study entry.
- Presence of cardiac pacemaker
- History or evidence of current ≥Class II congestive heart failure as defined by New York Heart Association (NYHA).
- History of acute coronary syndromes (including unstable angina and myocardial infarction), coronary angioplasty, or stenting within the past 3 months. Subjects with a history of stent placement requiring ongoing antithrombotic therapy (e.g., clopidogrel, prasugrel) will not be permitted to enroll.
- Clinically significant valvular disease, cardiomegaly, ventricular hypertrophy, or cardiomyopathy

Revised text:

11. Cardiac abnormalities as evidenced by any of the following:

- Baseline QTcF interval ≥450 msec
- Clinically significant conduction abnormalities or arrhythmia
- NOTE: Any clinically significant ECG assessments should be reviewed by the site cardiologist prior to study entry.
- Presence of cardiac pacemaker **or defibrillator with a paced ventricular rhythm limiting ECG analysis.**
- History or evidence of current ≥Class II congestive heart failure as defined by New York Heart Association (NYHA).
- History of acute coronary syndromes (including unstable angina and myocardial infarction), coronary angioplasty, or stenting within the past 3 months. Subjects with a history of stent placement requiring ongoing antithrombotic therapy (e.g., clopidogrel, prasugrel) will not be permitted to enroll.
- Clinically significant ~~valvular disease,~~ cardiomegaly, ventricular hypertrophy, or cardiomyopathy

Section 5.2. Exclusion Criteria

Addition of exclusion criteria around NSAID use and history of bleeding.

Previous text:

16. Hemoptysis >1 teaspoon in 24 hours within the last 28 days.

17. History of major gastrointestinal bleeding within the last 6 months.

18. Any clinically significant gastrointestinal (GI) abnormalities that may alter absorption, such as malabsorption syndrome, chronic gastrointestinal disease, or major resection of the stomach and/or bowels that could preclude adequate absorption of the study medication.

Revised text:

16. Hemoptysis >1 teaspoon in 24 hours within the last 28 days.
17. **Concurrent use of NSAIDs (except for cases where NSAIDs provide benefit over other analgesics and in these cases, consideration should be given to the prophylactic administration of a proton pump inhibitor) and high dose aspirin (allowed up to 100 mg PO daily). Details are available in Section 6.11.2.1.**
18. **Subjects with history of known bleeding disorder(s) including clinically significant hemorrhage (e.g., GI, neurologic), within the past 6 months.**~~History of major gastrointestinal bleeding within the last 6 months.~~
19. Any clinically significant gastrointestinal (GI) abnormalities that may alter absorption, such as malabsorption syndrome, chronic gastrointestinal disease, or major resection of the stomach and/or bowels that could preclude adequate absorption of the study medication.

Section 6.1. Investigational Product and Other Study Treatment

Clarification of what liquids GSK525762 may be taken with.

Previous text:

Dosing instructions:	Dose with 240 mL water and should be taken around the same time every day without regards to timing of meal (If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.)	Administer 500 mg intramuscularly into the buttocks slowly (1-2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29, and once monthly thereafter.

NOTE: The Phase 1 formulation details are current at the time of protocol finalization and may be updated in other documents (e.g., SRM and/or informed consent form) without requiring protocol amendment. Phase 2 formulation details will be provided in an amendment.

Revised text:

Dosing instructions:	Dose with 240 mL ~~water~~ **liquid*** and should be taken around the same time every day without regards to timing of meal (If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.)	Administer 500 mg intramuscularly into the buttocks slowly (1-2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29, and once monthly thereafter. **There is a ±3 day dosing window for the fulvestrant.**

NOTE: The Phase 1 formulation details are current at the time of protocol finalization and may be updated in other documents (e.g., SRM and/or informed consent form) without requiring protocol amendment. Phase 2 formulation details will be provided in an amendment.

***Subjects may take BET with 240 mL of liquid (other than orange, grapefruit, pomelo, or exotic citrus fruit juice). On serial PK days (W1D1 and W3D1), subjects must take BET with water only.**

Section 6.3. Planned Dose Adjustments

Addition of a dose reduction table to the Planned Dose Adjustments Section.

Previous text:

Subjects who experience toxicity may require dose delay and/or reduction of dose; for dose adjustment recommendations in response to toxicity, please refer to Appendix 2.

As described in Section 4.2.3.8, subjects receiving a dose below the RP2D at the end of Phase I may be dose escalated to a dose not to exceed the RP2D upon completion of Phase I.

Revised text:

Subjects who experience toxicity may require dose delay and/or reduction of dose; for dose adjustment recommendations in response to toxicity, please refer to Appendix 2. **Table 3 clarifies the dose reductions for GSK525762 at any planned dose level.**

As described in Section 4.2.3.8, subjects receiving a dose below the RP2D at the end of Phase I may be dose escalated to a dose not to exceed the RP2D upon completion of Phase I.

Table 3 GSK525762 Dose Reductions

Current GSK525762 Dose:	If subject requires dose level reduction:
40mg (DL-1)	No further dose reduction allowed
60mg (DL1)	40mg
80mg (DL2)	60mg

During any dose interruptions of GSK525762, fulvestrant may be continued at the protocol dose unless dose interruption of both products is required.

Section 6.10.2.2. Female Subjects of Childbearing Potential

Clarification around the acceptable failure rate of contraception used during the study.

Previous text:

Female subjects of childbearing potential must not become pregnant and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of <1% [Hatcher, 2011].

Revised text:

Female subjects of childbearing potential must not become pregnant and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of ≤<1% [Hatcher, 2011].

Section 6.11.2.1. Prohibited Medications

Clarification around NSAID and aspirin use during the study.

Previous text:

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

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

Revised text:

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

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

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

Section 6.11.2.1. Prohibited Medications

Update to the Prohibited Meds Table.

Previous text:

Table 3 Drugs with a Risk of Torsades de Pointes that are Prohibited

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

Data Source: crediblemeds.org revision date 17 Dec 2015. (Please refer to a database like crediblemeds.org for updates since these are dynamic lists that change based on new information which cannot be updated on a static table)

Revised text:

Table ~~3~~4 Drugs with a Risk of Torsades de Pointes that are Prohibited

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

Data Source: crediblemeds.org revision date **09 Jan**~~17 Dec~~ 201~~5~~. ~~(~~**The above table is not exhaustive.** Please refer to a database like crediblemeds.org for updates **at the time of screening a subject,** since these are dynamic lists that change based on new information which cannot be updated on a static table.~~)~~

Section 6.11.2.3. Cautionary Medications

Update to the Cautionary Meds Table.

Previous text:

If a subject requires medication for hyperemesis, due to the potential of serotonin 5-HT3 receptor antagonists to increase QT duration corrected for heart rate by Fridericia's formula (QTcF), palonosetron (up to a maximum dose of 0.25 mg daily) and ondansetron (up to a maximum dose of 8 mg three times daily [TID]) are the only allowed drugs in this class. Intravenous administration is not allowed. Drugs with a low risk of causing QTc prolongation (e.g., aprepitant) may be used without restriction.

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

Table ~~34~~ Drugs with a Risk of Torsades de Pointes which are permitted for co-administration with Extreme Caution

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

Data Source: crediblemeds.org revision date 17 Dec 2015. Please refer to a database like crediblemeds.org for updates since these are dynamic lists that change based on new information which cannot be updated on a static table

Revised text:

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

If a subject requires medication for hyperemesis, due to the potential of serotonin 5-HT3 receptor antagonists to increase QT duration corrected for heart rate by Fridericia's formula (QTcF), palonosetron (~~up to a maximum dose of 0.25 mg~~ **administered per the prescribing information**) and ondansetron (up to a maximum dose of 8 mg three times daily [TID]) are the only allowed drugs in this class. Intravenous administration is not allowed. Drugs with a low risk of causing QTc prolongation (e.g., aprepitant) may be used without restriction.

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

Table ~~15~~5 Drugs with a Risk of Torsades de Pointes which are permitted for co-administration with Extreme Caution

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

Data Source: crediblemeds.org revision date **09 Jan**~~17 Dec~~ 201~~7~~5. **The above table is not exhaustive.** Please refer to a database like crediblemeds.org for updates **at the time of screening a subject,** since these are dynamic lists that change based on new information which cannot be updated on a static table**.**

Section 7.2. Screening and Critical Baseline Assessments

Update to the time window for screening assessments.

Previous text:

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5. Medical, surgical, and treatment history including date of first diagnosis, best response to prior systemic therapy, histology, and current sites of disease will be taken as part of the medical history and disease status. Measurement(s) of target lesion(s) should be provided for at least two prior disease evaluations, if available. Details concerning concomitant medication will be recorded starting from screening through post-study follow-up. At a minimum, the drug name, route of administration, dose and frequency of dosing, along with start and stop dates should be recorded.

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

Revised text:

Screening procedures should be performed as rapidly as possible within 14 days prior to Day 1 (first dose of study medication) to facilitate subject entry requirements. In case of abnormal test values, retesting may be performed if medically indicated and within 14 days prior to Day 1.

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5. Medical, surgical, and treatment history including date of first diagnosis, best response to prior systemic therapy, histology, and current sites of disease will be taken as part of the medical history and disease status. Measurement(s) of target lesion(s) should be provided for at least two prior disease evaluations, if available. Details concerning concomitant medication will be recorded starting from screening through post-study follow-up. At a minimum, the drug name, route of administration, dose and frequency of dosing, along with start and stop dates should be recorded.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging studies, etc.) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed **14 days prior to Day 1 (first dose of study medication) unless otherwise indicated: CT scans (within 30 days prior to Day 1) and ECHO/MUGA (within 35 days prior to Day 1)** ~~in the timeframe of the study.~~

Section 7.2.1. Critical Baseline Assessments

Update to the time window for screening assessments.

Previous text:

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

- All subjects should have a contrast-enhanced (oral and IV) CT scan of the chest, abdomen, and pelvis performed. Baseline characterization of target- and non-target lesions should be performed as described in Appendix 7. For subjects with a contraindication to contrast-enhanced CT (e.g., documented allergy to iodinated contrast), then other modalities, such as non-enhanced CT of the chest and gadolinium-enhanced magnetic resonance imaging (MRI) of the abdomen and pelvis, may be used after discussion with the medical monitor. At each post-baseline assessment, re-evaluation of the site(s) of disease identified by these scans, using the same imaging modality, is required.

Revised text:

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

- All subjects should have a contrast-enhanced (oral and IV) CT scan of the chest, abdomen, and pelvis performed. **Baseline imaging should be completed within 30 days prior to the first dose of study drug.** Baseline characterization of target- and non-target lesions should be performed as described in Appendix 7. For subjects with a contraindication to contrast-enhanced CT (e.g., documented allergy to iodinated contrast), then other modalities, such as non-enhanced CT of the chest and gadolinium-enhanced magnetic resonance imaging (MRI) of the abdomen and pelvis, may be used after discussion with the medical monitor. At each post-baseline assessment, re-evaluation of the site(s) of disease identified by these scans, using the same imaging modality, is required.

Section 7.2.2. Visit Windows

Update to the visit windows.

Previous text:

Screening (baseline to pre-dose): Screening echocardiogram or MUGA scan should be completed within 35 days prior to the first dose of study drugs. All other assessments (including baseline imaging) should be completed within 14 days prior to first dose of study drugs. Clinical labs performed during screening within 72 hours of first dose do not need to be repeated on Day 1.

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

Week 3: Assessments on Week 3 Day 1 may be delayed up to 2 days. Assessments on Week 3 Day 4 may be scheduled ± 2 days.

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

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

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

Revised text:

Screening (baseline to pre-dose): Screening echocardiogram or MUGA scan should be completed within 35 days prior to the first dose of study drugs. **Baseline imaging should be completed within 30 days prior to the first dose of study drug.** All other assessments ~~(including baseline imaging)~~ should be completed within 14 days prior to first dose of study drugs. Clinical labs performed during screening within 72 hours of first dose do not need to be repeated on Day 1.

Week 2: Based on subject and clinic schedule, assessments can be ± **3**~~2~~ days.

Week 3: Assessments on Week 3 Day 1 may be delayed up to 2 days. Assessments on Week 3 Day 4 may be scheduled ± **3**~~2~~ days.

Weeks 4, 5, and 9: Clinic visits may be scheduled ± **3**~~2~~ days. The first disease assessment (at Week 9) may be scheduled ± 7 days.

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

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

Section 7.3.4. Clinical Safety Laboratory Assessments

Update to the Clinical Laboratory Tests Table.

Previous text:

Table 9 Clinical Laboratory Tests

Coagulation Studies:	**Endocrine Studies:**	**Safety Screening Studies:**
Prothrombin Time/INR	Thyroid-stimulating hormone (TSH)	Pregnancy test (serum at screening, Urine or serum post dose)
Partial Thromboplastin Time	Free Thyroxine 3 (Free T3)	HIV, HbSag, HCV antibody
Fibrinogen	Free Thyroxine 4 (Free T4)	**Pancreatic Markers:**
	Hemoglobin A1c	Amylase
	FSH and estradiol (for pre- and peri-menopausal subjects only)	Lipase

Revised text:

Table ~~9~~10 Clinical Laboratory Tests

Coagulation Studies:	**Endocrine Studies:**	**Safety Screening Studies:**
Prothrombin Time/INR	Thyroid-stimulating hormone (TSH)	~~Pregnancy test (serum at screening, Urine or serum post dose)~~
Partial Thromboplastin Time	Free Thyroxine 3 (Free T3)	HIV, HbSag, HCV antibody
Fibrinogen	Free Thyroxine 4 (Free T4)	**Pancreatic Markers:**
Factor VII Assay	Hemoglobin A1c	Amylase
	FSH and estradiol (for pre- and peri-menopausal subjects only)	Lipase

Section 7.3.5.1. Time period and Frequency for collecting AE and SAE information

Clarification of whom needs to be notified of AEs or SAEs

Previous text:

- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 10.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

Revised text:

- All SAEs will be recorded and reported to GSK **or designee** within 24 hours, as indicated in Appendix 10.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK **or designee**.

Section 7.5.1. Tumor Biopsy Collection/Surgical Procedures

Updated title of the section and provided guidance added around amount of dosing needed prior to fresh biopsy collection, and required platelet counts for subjects prior to fresh biopsy collection.

Previous text:

Section 7.5.1. Tumor Biopsy Collection

In Phase I, paired fresh biopsies must be provided pre- (within 14 days of the first dose) and on-treatment at the time points indicated for at least 6 subjects (out of 35 planned for enrollment) at each dose level. A limited number of additional subjects may be requested to provide pre and on-treatment biopsies based on emerging data. Biopsy requirement(s) will be discussed with the subject prior to signing informed consent. Any fresh ontreatment biopsy should be accompanied by a plasma sample collected as close as possible to the time of biopsy (preferably within 1 h). Further details regarding sample type and processing will be provided in the SRM.

Revised text:

Section 7.5.1. Tumor Biopsy Collection/Surgical Procedures

In Phase I, paired fresh biopsies must be provided pre- (within 14 days of the first dose) and on-treatment at the time points indicated for at least 6 subjects (out of 35 planned for enrollment) at each dose level. **Subjects providing an on-treatment fresh tumor biopsy must have received at least 4 consecutive doses of GSK525762 prior to the collection of the tissue.** A limited number of additional subjects may be requested to provide pre and on-treatment biopsies based on emerging data. Biopsy requirement(s) will be discussed with the subject prior to signing informed consent. Any fresh on-treatment biopsy should be accompanied by a plasma sample collected as close as possible to the time of biopsy (preferably within 1 h).

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

Section 7.6. Evaluation of Anti-Cancer Activity

Update to the time window for screening assessments.

Previous text:

The baseline disease assessment will be completed within 14 days prior to the first dose of GSK525762 and fulvestrant, then approximately every 8 weeks thereafter and at the final study visit. See the Time and Events Table (Section 7.1) for the schedule of assessments of anti-cancer activity.

Revised text:

The baseline disease assessment will be completed within ~~14~~ **30** days prior to the first dose of GSK525762 and fulvestrant, then approximately every 8 weeks thereafter and at the final study visit. See the Time and Events Table (Section 7.1) for the schedule of assessments of anti-cancer activity.

Appendix 2 Management of Suspected Toxicity

Table 13 Dose Adjustment/Stopping Safety Criteria

Update to the Thrombocytopenia toxicity management guidelines.

Previous text:

Table 12 Dose Adjustment/Stopping Safety Criteria

Thrombocytopenia	Grade 1 & 2	Continue dosing at same dose level with weekly or more frequent monitoring as necessary
	Grade 3 (platelets <50,000, ≥25,000/mm^3)	Withhold GSK525762 and check aPTT, PT, and INR. Monitor CBC and coagulation studies at least twice a week, or more frequently if clinically indicated. Hold GSK525762 until thrombocytopenia has resolved to ≤ Grade 2 AND aPTT, PT, and INR are all ≤ ULN. Drug may then be restarted at the same dose or at a lower dose level, after discussion with medical monitor. If safety lab abnormalities recur following rechallenge, drug may be discontinued or restarted at a lower dose level, after discussion with medical monitor. As per the fulvestrant package insert, because fulvestrant is administered intramuscularly, it should be used with caution in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use.
	Grade 4 (platelets <25,000/mm^3), or any moderate to severe bleeding accompanied by drug related thrombocytopenia	Withhold GSK525762 and check aPTT, PT, and INR. Monitor CBC and coagulation studies every 2-3 days. Hold GSK525762 until thrombocytopenia has resolved to ≤ Grade 2 AND aPTT, PT, and INR are all ≤ ULN. Drug may then be restarted at a lower dose level, after discussion with medical monitor. If safety lab abnormalities recur following rechallenge, drug may be discontinued until platelet count recovers to Grade 2 (≥50,000 u/l). As per the fulvestrant package insert, because fulvestrant is administered intramuscularly, it should be used with caution in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use. For subjects with moderate to severe bleeding requiring transfusion support, GSK525762 should be permanently discontinued. If platelet count does not recover to ≥50,000/ u/l (Grade 2) within 14 days, GSK525762 should be permanently

		discontinued. If platelet count recovers to ≥50,000/ u/l (Grade 2) within 14 days, GSK525762 may be continued at the current/ reduced dose after discussion with the medical monitor.

Revised text:

Table 13~~12~~ Dose Adjustment/Stopping Safety Criteria

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Thrombocytopenia	Grade 1 **(platelets <LLN to ≥75,000/mm^3)** & **Grade** 2 **(platelets <75,000 to ≥50,000/mm^3)**	Continue dosing at same dose level with weekly or more frequent monitoring as necessary
	Grade 3 (platelets <50,000, ≥25,000/mm^3)	Withhold GSK525762 and check aPTT, PT, and INR. Monitor CBC and coagulation studies at least twice a week, or more frequently if clinically indicated. Hold GSK525762 until thrombocytopenia has resolved to ≤ Grade 2 AND aPTT, PT, and INR are all ≤ ULN. Drug may then be restarted ~~at the same dose or~~ at **a** ~~lower~~ dose level **lower**, after discussion with medical monitor. If safety lab abnormalities recur following rechallenge, drug may be discontinued or restarted at a**nother dose level** lower ~~dose level~~, after discussion with medical monitor. **If safety lab abnormalties recur at the same dose level following a second rechallenge, GSK525762 should be permanently discontinued.** As per the fulvestrant package insert, because fulvestrant is administered intramuscularly, it should be used with caution in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use.
	Grade 4 (platelets <25,000/mm^3), or any moderate to severe bleeding accompanied by drug related thrombocytopenia	Withhold GSK525762 and check aPTT, PT, and INR. Monitor CBC and coagulation studies every 2-3 days. Hold GSK525762 until thrombocytopenia has resolved to ≤ Grade 2 AND aPTT, PT, and INR are all ≤ ULN. Drug may then be restarted at a lower dose level, after discussion with medical monitor. If safety lab abnormalities recur following rechallenge, drug may be discontinued until platelet count recovers to Grade 2 (≥50,000 **mm^3**~~u/l~~). As per the fulvestrant package insert, because fulvestrant is administered intramuscularly, it should be used with caution in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use. For subjects with moderate to severe bleeding requiring transfusion support, GSK525762 should be permanently discontinued. If platelet count does not recover to ≥50,000/ **mm^3**~~u/l~~ (Grade 2) within 14 days, GSK525762 should be permanently discontinued.

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
		If platelet count recovers to ≥50,000/**mm³~~u~~l** (Grade 2) within 14 days, GSK525762 may be continued at the current/ reduced dose after discussion with the medical monitor. **If platelet count does not recover to ≥25,000/ mm³ (Grade 3) within 7 days, GSK525762 should be permanently discontinued.**

Section Appendix 4: 12.4.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

Clarification around acceptable methods of contraception, and length of time they need to be used.

Previous text:

1. Intrauterine device (IUD) or intrauterine system
2. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

Note: Hormonal methods of contraception are not permitted since the efficacy of these methods in combination with GSK525762 has not been assessed. Hormone-releasing IUDs are a permitted form of contraception. LHRH-acting agents alone are not considered an adequate form of contraception. GSK525762 has been shown to effect female reproductive systems in animals, therefore women of childbearing potential should adhere to this contraceptive guidance whilst on study and for 7 months after cessation of treatment with GSK525762.

Revised text:

1. **Non-hormonal i~~I~~**ntrauterine device (IUD) or intrauterine system **(IUS) that meets the ≤1% failure rate as stated in the product label**
2. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

Note: Hormonal methods of contraception are not permitted since the efficacy of these methods in combination with GSK525762 has not been assessed. ~~Hormone-releasing IUDs are a permitted form of contraception.~~ LHRH-acting agents alone are not considered an adequate form of contraception. **GSK525762 has been shown to effect female reproductive systems in animals, therefore women of childbearing potential**

should adhere to this contraceptive guidance whilst on study and for 7 months after cessation of treatment with GSK525762.

Section 12.7.1. Baseline Documentation of Target and Non-Target Lesions

Removal of baseline brain scan wording that should have been removed in amendment 02.

Previous text:

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

Revised text:

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

Other Protocol Changes

Addition of Table 3 in this section, which has resulted in the change of Table Numbers in the following sections.

Section 12.1. Appendix 1: Abbreviations and Trademarks

Addition of new abbreviation

Addition of SERD (Selective Estrogen Receptor Degrader) in the abbreviations list.

Section 7.1 Time and Events Table

Update to the T&E tables to reflect assessment changes or additions.

Previous text

Table 5 Time and Events, Phase I

Procedure	SCR	Week 1		Week 2		Week 3		Week 4	Week 5	q4w	q8w	EOT[1]
		D1	D4	D1	D4	D1	D4	D1	D1	W9 and thereafter	W9 and thereafter	
Screening[2]												
Informed Consent	X											
Demography	X											
Medical History	X											
Inclusion/Exclusion Criteria	X											
Disease Characteristics	X											
Prior Therapy[3]	X											
Register Subject	X											
Safety												
Physical Exam[4]	X	X		X		X		X	X	X		X
ECOG PS	X	X		X		X		X	X	X		X
12-lead ECGs (Triplicate)[5]	X	X	X	X		X		X	X	X		X
Clinical Laboratory Assessments[6]	X	X	X	X	X	X	X	X	X	X		X
Echocardiogram or MUGA[7]	X								X		X	X
PRO-CTCAE[8]	X	X		X		X		X	X	X		X
Study Treatment												
Administer GSK525762[9]		Daily										
Administer Fulvestrant[9]		X				X			X	X		
AE/SAE review		Continuous from signing of informed consent										
Concomitant medication review		Continuous from signing of informed consent										
Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)												
PK blood samples[10]		PK				PK			O		X	
Tumor biopsy[11]	X					One sample, collected between W3D1 and W4D1, as close as possible to 3-6h post-GSK525762 dose,						X[12]
Whole blood for exploratory analyses	X							X				X
PGx blood sample		X										
Efficacy												

Procedure	SCR	Week 1		Week 2		Week 3		Week 4	Week 5	q4w	q8w	EOT [1]
		D1	D4	D1	D4	D1	D4	D1	D1	W9 and thereafter	W9 and thereafter	
CT chest/abdomen/pelvis[13]	X										X	X
EORTC-QLQ-C30 & EORTC-QLQ-BR23[14]	X	X		X		X		X	X	X		X

1. Applies to subjects who withdraw for any reason prior to progression or who progress during study treatment. Following this visit, subjects will be contacted approximately every 3 months (± 14 days) to collect: survival status as of last date of contact and initiation of new anti-cancer therapy. Contact may be completed via a clinic visit, a telephone contact or an email.
2. Screening echocardiograms should be completed within 35 days prior to the first dose of study drugs. All other assessments (including baseline imaging) should be completed within 14 days prior to first dose of study drugs.
3. Including dates of imaging and sizes of target lesion(s) used for RECIST 1.1 evaluation, if available.
4. Complete physical examination required at screening, Week (W)1 Day (D)1 (W1D1), and end of the treatment (EOT) visits. Limited examinations permitted at all other visits, as noted. Definition of complete and limited examinations may be found in Section 7.3.1.
5. Triplicate ECGs should be performed prior to dosing and evaluated for abnormality prior to administration of dose.
6. Refer to Table 7 for details of clinical safety labs and timing of collection
7. Whatever scanning modality is used at screening should be maintained for all subsequent scans.
8. Patient Reported Outcomes Version of the Common a Terminology Criteria for Adverse Events (PRO-CTCAE) Item Library (Version 1.0)
9. Drugs should be administered as described in Section 6.1. Visits where fulvestrant is administered will be considered drug dispensing days. On PK collection days in Week 1 and Week 3, subjects should abstain from food from 8 h prior until 2 h after dose as described in Section 6.10.1
10. "PK" = serial PK days. Sample collections should be obtained at the following timepoints: Pre-dose, 30 m ± 5 m, 1 h ± 10 m, 3 h ± 30 m. "O" = sample collections to be obtained pre-dose, 0.5-1h post-dose, and an optional sample 4-8h post-dose. "X" = sample collections to be obtained pre-dose as well as 0.5-1h post-dose (note that routine PK is no longer required once the subject has been on study for 26 weeks). Pre-dose samples will be split to obtain a PK sample for fulvestrant analysis. Refer to the SRM for further details.
11. Screening (archival) tumor biopsy specimen required for all subjects; if archival sample is not available then fresh specimen must be provided as described in Section 7.7.2. Paired fresh biopsies must be provided pre- and on-treatment at the time points indicated for at least 6 subjects (out of 35 planned for enrollment) at each dose level. A limited number of additional subjects may be requested to provide pre and on-treatment biopsies based on emerging data. Fresh biopsies should be paired with plasma samples for PK, collected as close as possible to biopsy (ideally within 1 h). Refer to the SRM for further details.
12. A tumor biopsy at the end of treatment is optional.
13. CT should be performed with oral and intravenous (IV) contrast. CT required at screening. Any potential CR or PR should be confirmed as described in Appendix 7. EOT disease assessment is not required if reason for discontinuing therapy was progressive disease and prior assessment was within 14 days of EOT visit. Subjects with contraindication to contrast-enhanced computed tomography (CT) may have other imaging performed as described in Section 7.2.1.
14. European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core-30 and Breast 23 measures.

Revised text

Table ~~5~~6 Time and Events, Phase I

Procedure	SCR	Week 1		Week 2		Week 3		Week 4	Week 5	q4w	q8w	q8w	EOT[1]
		D1	D4	D1	D4	D1	D4	D1	D1	W9 ~~and therea fterto~~ W49	W9 ~~and therea fterto~~ W49	W49 and therea fter	
Screening[2]													
Informed Consent	X												
Demography	X												
Medical History	X												
Inclusion/Exclusion Criteria	X												
Disease Characteristics	X												
Prior Therapy[3]	X												
Register Subject	X												
Safety													
Physical Exam[4]	X	X		X		X		X	X	X			X
ECOG PS	X	X		X		X		X	X	X			X
12-lead ECGs (Triplicate)[5]	X	X	X	X		X		X	X	X			X
Clinical Laboratory Assessments[6]	X	X	X	X	X	X	X	X	X	X			X
Echocardiogram or MUGA[7]	X	**X**							X	**Week 13, 25, 37, 49**	X		X
PRO-CTCAE[8]	X	X		X		X		X	X	X		**X**	X
Study Treatment													
Administer GSK525762[9]		Daily											
Administer Fulvestrant[9]		X				X			X	X			
AE/SAE review		Continuous from signing of informed consent											
Concomitant medication review		Continuous from signing of informed consent											
Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)													
PK blood samples[10]		PK				PK			O		X		
Tumor biopsy[11]	X					One sample, collected between W3D1 and W4D1, as close as possible to 3-6h post-GSK525762 dose							X[12]
Whole blood for exploratory analyses	X							X					X
PGx blood sample		X											

Procedure	SCR	Week 1		Week 2		Week 3		Week 4	Week 5	q4w	q8w	q8w	EOT[1]
		D1	D4	D1	D4	D1	D4	D1	D1	W9 ~~and thereafterto~~ W49	W9 ~~and thereafterto~~ W49	W49 and thereafter	
Efficacy													
CT chest/abdomen/pelvis[13]	X										X	**X**	X
EORTC-QLQ-C30 & EORTC-QLQ-BR23[14]	X	X		X		X		X	X	X		**X**	X

1. Applies to subjects who withdraw for any reason prior to progression or who progress during study treatment. Following this visit, subjects will be contacted approximately every 3 months (± 14 days) to collect: survival status as of last date of contact and initiation of new anti-cancer therapy. Contact may be completed via a clinic visit, a telephone contact or an email.
2. ~~Screening echocardiograms should be completed within 35 days prior to the first dose of study drugs. All other assessments (including baseline imaging) should be completed within 14 days prior to first dose of study drugs.~~**Screening procedures should be performed as rapidly as possible within 14 days prior to Day 1 (first dose of study medication) to facilitate subject entry requirements. In case of abnormal test values, retesting may be performed if medically indicated and within 14 days prior to Day 1. Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging studies, etc.) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within 14 days prior to Day 1 (first dose of study medication) unless otherwise indicated: CT scans (within 30 days prior to Day 1) and ECHO/MUGA (within 35 days prior to Day 1)**.
3. Including dates of imaging and sizes of target lesion(s) used for RECIST 1.1 evaluation, if available.
4. Complete physical examination required at screening, Week (W)1 Day (D)1 (W1D1), and end of the treatment (EOT) visits. Limited examinations permitted at all other visits, as noted. Definition of complete and limited examinations may be found in Section 7.3.1.
5. Triplicate ECGs should be performed prior to dosing and evaluated for abnormality prior to administration of dose.
6. Refer to ~~Table~~ 7 **Table 7** for details of clinical safety labs and timing of collection
7. Whatever scanning modality is used at screening should be maintained for all subsequent scans. **Beginning at W13, scans will be performed once every 12 weeks.**
8. Patient Reported Outcomes Version of the Common a Terminology Criteria for Adverse Events (PRO-CTCAE) Item Library (Version 1.0). **Post Week 49, assessments will be completed every 8 weeks.**
9. Drugs should be administered as described in Section 6.1. Visits where fulvestrant is administered will be considered drug dispensing days. **There is a ±3 day window for fulvestrant dosing.** On PK collection days in Week 1 and Week 3, subjects should abstain from food from 8 h prior until 2 h after dose as described in Section 6.10.1. **Post Week 49, fulvestrant will continue to be administered every 4 weeks. Refer to the SRM for further details.**
10. "PK" = serial PK days. Sample collections should be obtained at the following timepoints: Pre-dose, 30 m ± 5 m, 1 h ± 10 m, 3 h ± 30 m. "O" = sample collections to be obtained pre-dose, 0.5-1h post-dose, and an optional sample 4-8h post-dose. "X" = sample collections to be obtained pre-dose as well as 0.5-1h post-dose (note that routine PK is no longer required once the subject has been on study for 26 weeks). Pre-dose samples will be split to obtain a PK sample for fulvestrant analysis. Refer to the SRM for further details.
11. Screening (archival) tumor biopsy specimen required for all subjects; if archival sample is not available then fresh specimen must be provided as described in Section 7.7.2. Paired fresh biopsies must be provided pre- and on-treatment at the time points indicated for at least 6 subjects (out of 35 planned for enrollment) at each dose level. **Subjects providing an on-treatment fresh tumor biopsy must have received at least 4 consecutive doses of GSK525762 prior to the collection of the tissue. If the post-dose biopsy is not performed during this timeframe due to lab abnormalities or subject status, it should be performed at the next agreed upon visit with the medical monitor after subject recovery.** A limited number of additional subjects may be

requested to provide pre and on-treatment biopsies based on emerging data. Fresh biopsies should be paired with plasma samples for PK, collected as close as possible to biopsy (ideally within 1 h). **Subjects must have a platelet count of ≥75,000/mm^3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy, or any other planned surgical procedure.**Refer to the SRM for further details.

12. A tumor biopsy at the end of treatment is optional.
13. CT should be performed with oral and intravenous (IV) contrast. CT required at screening. Any potential CR or PR should be confirmed as described in Appendix 7. EOT disease assessment is not required if reason for discontinuing therapy was progressive disease and prior assessment was within 14 days of EOT visit. Subjects with contraindication to contrast-enhanced computed tomography (CT) may have other imaging performed as described in Section 7.2.1.
14. European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core-30 and Breast 23 measures. **Post Week 49, assessments will be completed every 8 weeks.**

Previous Text:

Table 6 Time and Events, Phase I Laboratory Assessments

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

1. Only required at screening for pre- and peri-menopausal subjects

2. Serum pregnancy test within 7 days prior to first dose; urine or serum test thereafter

Revised text

Table 7~~6~~ Time and Events, Phase I Laboratory Assessments

	SCR	**Week 1**		**Week 2**		**Week 3**		**Week 4**	**Week 5**	**Week 7**	**~~q4w~~Week 9**	**Week 11**	**q4w**	**EOT**
		D1	**D4**	**D1**	**D4**	**D1**	**D4**	**D1**	**D1**	**D1**	**~~W19 and thereafter~~D1**	**D1**	**W13 and thereafter**	
Clinical chemistry	X	X	X	X		X		X	X	**X**	X	**X**	**X**	X
Hematology	X	X	X	X	X	X	X	X	X	**X**	X	**X**	**X**	X
Liver chemistry	X	X	X	X	X	X	X	X	X	**X**	X	**X**	**X**	X
Troponin, N-terminal pro–B-Type natriuretic peptide (NT-proBNP)	X	X	X	X	X	X	X	X	X	**X**	X	**X**	**X**	X
Coagulation	X	X	X	X		X		X	X	**X**	X	**X**	**X**	X
Factor VII Assay[1]	**X**					**X**			**X**					
Fasting blood glucose	X	X	X	X		X		X	X	**X**	X	**X**	**X**	X
HbA1c	X								X	**X**	X	**X**	**X**	X
Fasting lipids	X								X	**X**	X	**X**	**X**	X
Thyroid (Thyroid stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4))	X								X	**X**	X	**X**	**X**	X
Pancreatic	X	X		X		X		X	X	**X**	X	**X**	**X**	X
Urinalysis	X	X		X		X		X	X	**X**	X	**X**	**X**	X
HIV, Hepatitis B surface antigen (HBsAg), Hepatitis C Virus (HCV) Antibody	X													

	SCR	**Week 1**		**Week 2**		**Week 3**		**Week 4**	**Week 5**	**Week 7**	**~~q4w~~Week 9**	**Week 11**	**q4w**	**EOT**
		D1	**D4**	**D1**	**D4**	**D1**	**D4**	**D1**	**D1**	**D1**	**~~W19 and thereafter~~D1**	**D1**	**W13 and thereafter**	
FSH/Estradiol[2]	X													
Pregnancy test[3]	X	X				**X**			X	**X**	X	**X**	**X**	X

1. **Also perform if PT or INR are ≥1.5XULN, or in case of bleeding event**
2. Only required at screening for pre- and peri-menopausal subjects
3. Serum pregnancy test within 7 days prior to first dose; urine or serum test thereafter

Previous text

Table 7 Time and Events, Phase II

Procedure	SCR	Week 1		Week 2	Week 3	Week 4	Week 5	q4w	q8w	EOT[1]
		D1	D4	D1	D1	D1	D1	W9 and thereafter	W9 and thereafter	
Screening[2]										
Informed Consent	X									
Demography	X									
Medical History	X									
Inclusion/Exclusion Criteria	X									
Disease Characteristics	X									
Prior Therapy[3]	X									
Register Subject	X									
Safety										
Physical Exam[4]	X	X		X	X	X	X	X		X
ECOG PS	X	X		X	X	X	X	X		X
12-lead ECGs (Triplicate)[5]	X	X	X	X	X	X	X	X		X
Clinical Laboratory Assessments[6]	X	X	X	X	X	X	X	X		X
Echocardiogram or MUGA[7]	X								X	X
PRO-CTCAE[8]	X	X		X	X	X	X	X		X
Study Treatment										
Administer GSK525762[9]		Daily								
Administer Fulvestrant[9]		X			X		X	X		
AE/SAE review		Continuous from signing of informed consent								
Concomitant medication review		Continuous from signing of informed consent								
Pharmacokinetics (PK), Translational Studies & Pharmacogenomics (PGx)										
PK blood samples[10]		O					O		X	
Tumor biopsy (archival)[11]	X									X[12]
Whole blood for exploratory analyses	X					X				X
PGx blood sample		X								
Efficacy										
CT chest/abdomen/pelvis[13]	X								X	X
EORTC-QLQ-C30 & EORTC-QLQ-BR23[14]	X	X		X	X	X	X	X		X

1. Applies to subjects who withdraw for any reason prior to progression or who progress during study treatment. Following this visit, subjects will be contacted approximately every 3 months (± 14 days) to collect: survival status as of last date of contact and initiation of new anti-cancer therapy. Contact may be completed via a clinic visit, a telephone contact or an email.
2. Screening echocardiograms should be completed within 35 days prior to the first dose of study drugs. All other assessments (including baseline imaging) should be completed within 14 days prior to first dose of study drugs.
3. Including dates of imaging and sizes of target lesion(s) used for RECIST 1.1 evaluation, if available.
4. Complete physical examination required at screening, Week (W)1 Day (D)1 (W1D1), and end of the treatment (EOT) visits. Limited examinations permitted at all other visits, as noted. Definition of complete and limited examinations may be found in Section 7.3.1.
5. Triplicate ECGs should be performed prior to dosing and evaluated for abnormality prior to administration of dose.
6. Refer to Table 9 for details of clinical safety labs and timing of collection
7. Whatever scanning modality is used at screening should be maintained for all subsequent scans.
8. Patient Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Item Library (Version 1.0)
9. Drugs should be administered as described in Section 6.1. Visits where fulvestrant is administered will be considered drug dispensing days.
10. "O" = sample collections to be obtained pre-dose, 0.5-1h post-dose, and an optional sample 4-8h post-dose. "X" = sample collections to be obtained pre-dose as well as 0.5-1h post-dose (note that routine PK is no longer required once the subject has been on study for 26 weeks). Pre-dose samples will be split to obtain a PK sample for fulvestrant analysis only for subjects who are receiving fulvestrant. Refer to the SRM for further details.
11. Screening (archival) tumor biopsy specimen required for all subjects; if archival sample is not available then fresh specimen must be provided. Refer to Section 7.2.1 and to the SRM for further details.
12. Tumor biopsy at the end of treatment is optional.
13. CT should be performed with oral and intravenous (IV) contrast. Any potential CR or PR should be confirmed as described in Appendix 7. EOT disease assessment is not required if reason for discontinuing therapy was progressive disease and prior assessment was within 14 days of EOT visit. Subjects with contraindication to contrast-enhanced computed tomography (CT) may have other imaging performed as described in Section 7.2.1.
14. European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core-30 and Breast 23 measures.

Revised text

Table ~~7~~8 Time and Events, Phase II

Procedure	SCR	Week 1		Week 2	Week 3	Week 4	Week 5	q4w	q8w	q8w	EOT[1]
		D 1	D 4	D1	D1	D1	D1	W9 ~~and there after~~ o W49	W9 ~~and there after~~ o W49	W49 and therea fter	
Screening[2]											
Informed Consent	X										
Demography	X										
Medical History	X										
Inclusion/Exclusion Criteria	X										
Disease Characteristics	X										
Prior Therapy[3]	X										
Register Subject	X										
Safety											
Physical Exam[4]	X	X		X	X	X	X	X			X
ECOG PS	X	X		X	X	X	X	X			X
12-lead ECGs (Triplicate)[5]	X	X	X	X	X	X	X	X			X
Clinical Laboratory Assessments[6]	X	X	X	X	X	X	X	X			X
Echocardiogram or MUGA[7]	X	**X**					**X**	**Week 13, 25, 37, 49**	~~X~~		X
PRO-CTCAE[8]	X	X		X	X	X	X	X		**X**	X
Study Treatment											
Administer GSK525762[9]		Daily									
Administer Fulvestrant[9]		X			X		X	X			
AE/SAE review		Continuous from signing of informed consent									
Concomitant medication review		Continuous from signing of informed consent									
Pharmacokinetics (PK), Translational Studies & Pharmacogenomics (PGx)											
PK blood samples[10]		O					O		X		
Tumor biopsy (archival)[11]	X										X[12]
Whole blood for exploratory analyses	X					X					X
PGx blood sample		X									
Efficacy											
CT chest/abdomen/pelvis[13]	X								X	**X**	X
EORTC-QLQ-C30 & EORTC-QLQ-BR23[14]	X	X		X	X	X	X	X		**X**	X

1. Applies to subjects who withdraw for any reason prior to progression or who progress during study treatment. Following this visit, subjects will be contacted approximately every 3 months (± 14 days) to collect: survival status as of last date of contact and initiation of new anti-cancer therapy. Contact may be completed via a clinic visit, a telephone contact or an email.
2. ~~Screening echocardiograms should be completed within 35 days prior to the first dose of study drugs. All other assessments (including baseline imaging) should be completed within 14 days prior to first dose of study drugs.~~ **Screening procedures should be performed as rapidly as possible within 14 days prior to Day 1 (first dose of study medication) to facilitate subject entry requirements. In case of abnormal test values, retesting may be performed if medically indicated and within 14 days prior to Day 1. Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging studies, etc.) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within 14 days prior to Day 1 (first dose of study medication) unless otherwise indicated: CT scans (within 30 days prior to Day 1) and ECHO/MUGA (within 35 days prior to Day 1).**
3. Including dates of imaging and sizes of target lesion(s) used for RECIST 1.1 evaluation, if available.
4. Complete physical examination required at screening, Week (W)1 Day (D)1 (W1D1), and end of the treatment (EOT) visits. Limited examinations permitted at all other visits, as noted. Definition of complete and limited examinations may be found in Section 7.3.1.
5. Triplicate ECGs should be performed prior to dosing and evaluated for abnormality prior to administration of dose.
6. Refer to ~~Table 8~~**Table 9** for details of clinical safety labs and timing of collection
7. Whatever scanning modality is used at screening should be maintained for all subsequent scans. **Beginning at W13, scans will be performed once every 12 weeks.**
8. Patient Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Item Library (Version 1.0). **Post Week 49, assessments will be completed every 8 weeks.**
9. Drugs should be administered as described in Section 6.1**.** Visits where fulvestrant is administered will be considered drug dispensing days. **There is a ±3 day window for the fulvestrant dosing. Post Week 49, fulvestrant will continue to be administered every 4 weeks. Refer to the SRM for further details.**
10. "O" = sample collections to be obtained pre-dose, 0.5-1h post-dose, and an optional sample 4-8h post-dose. "X" = sample collections to be obtained pre-dose as well as 0.5-1h post-dose (note that routine PK is no longer required once the subject has been on study for 26 weeks). Pre-dose samples will be split to obtain a PK sample for fulvestrant analysis only for subjects who are receiving fulvestrant. Refer to the SRM for further details.
11. Screening (archival) tumor biopsy specimen required for all subjects; if archival sample is not available then fresh specimen must be provided. Refer to Section 7.2.1 and to the SRM for further details. **Subjects must have a platelet count of ≥75,000/mm^3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy, or any other planned surgical procedure.**
12. Tumor biopsy at the end of treatment is optional.
13. CT should be performed with oral and intravenous (IV) contrast. Any potential CR or PR should be confirmed as described in Appendix 7. EOT disease assessment is not required if reason for discontinuing therapy was progressive disease and prior assessment was within 14 days of EOT visit. Subjects with contraindication to contrast-enhanced computed tomography (CT) may have other imaging performed as described in Section 7.2.1.
14. European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core-30 and Breast 23 measures. **Post Week 49, assessments will be completed every 8 weeks.**

Previous text

Table 8 Time and Events, Phase 2 Laboratory Assessments

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

1. Only required at screening for pre- and peri-menopausal subjects
2. Serum pregnancy test within 7 days prior to first dose; urine or serum test thereafter

Revised Text

Table ~~8~~9 Time and Events, Phase 2 Laboratory Assessments

	SCR	**Week 1**		**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 7**	**~~q4w~~ Week 9**	**Week 11**	**q4w**	**EOT**
		D1	**D4**	**D1**	**D1**	**D1**	**D1**	**D1**	**~~W9 and thereafter~~ D1**	**D1**	**W13 and thereafter**	
Clinical chemistry	X	X	X	X	X	X	X	**X**	X	**X**	**X**	X
Hematology	X	X	X	X	X	X	X	**X**	X	**X**	**X**	X
Liver chemistry	X	X	X	X	X	X	X	**X**	X	**X**	**X**	X
Troponin, N-terminal pro–B-Type natriuretic peptide (NT-proBNP)	X	X	X	X	X	X	X	**X**	X	**X**	**X**	X
Coagulation	X	X	X	X	X	X	X	**X**	X	**X**	**X**	X
Factor VII Assay[1]	**X**				**X**		**X**					
Fasting blood glucose	X	X	X	X	X	X	X	**X**	X	**X**	**X**	X
HbA1c	X						X	**X**	X	**X**	**X**	X
Fasting lipids	X						X	**X**	X	**X**	**X**	X
Thyroid (Thyroid stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4))	X						X	**X**	X	**X**	**X**	X
Pancreatic	X	X		X	X	X	X	**X**	X	**X**	**X**	X
Urinalysis	X	X		X	X	X	X	**X**	X	**X**	**X**	X
HIV, Hepatitis B surface antigen (HBsAg), Hepatitis C Virus (HCV) Antibody	X											
FSH/Estradiol[2]	X											
Pregnancy test[3]	X	X			**X**		X	**X**	X	**X**	**X**	X

1. **Also perform if PT or INR are ≥1.5XULN, or in case of bleeding event**
2. Only required at screening for pre- and peri-menopausal subjects
3. Serum pregnancy test within 7 days prior to first dose; urine or serum test thereafter

12.14.4. Amendment 04

Protocol changes for Amendment 04, from protocol changes to amendment 03 (07-MAR-2017)

Amendment 04 summary:

Amendment 04 applies to all global study sites.

Changes to the protocol include:
Based upon review and comment on the protocol by the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), the following changes are being implemented: language added to Section 6.11.2.3 around concomitant medications that are substrates of CYP3A4; update to the toxicity management guidelines for QTcF monitoring in Appendix 2, Table 13; Times and Events tables in Section 7.1, updated to clarify the schedule of assessments post week 49.
Additional changes to the protocol include: update to protocol authors; update to the primary GSK medical monitor; update to Sponsor signatory; ERS1 mutational status in the objectives and endpoints has been updated to exploratory, and Section 7.7 has been updated to reflect the translational analysis changes; removal of the time to progression (TTP) endpoints; update to description of Ph I enrolment during the dose escalation phase and the definition of study completion in Ph II; update to statistical analysis descriptions throughout the protocol; addition of information around the dose escalation meetings; Section 6.6 on the handling of GSK525762; clarification in Section 5.1, Table 2, regarding acceptability of both Troponin I or T; Times and Events tables in Section 7.1, updated to clarify ECHO/MUGA scan requirements for screening and W1D1, timing of on treatment biopsy collection in Ph I, lab assessment requirements, and length of screening window (also updated throughout the document); update to the toxicity management guidelines for QTcF re-challenge in Appendix 2, Table 13; removal of pre-defined events of interest.

List of Specific Changes

Title Page

Updated protocol author list

Previous text:

PPD

Revised text:

PPD

Sponsor Signatory

Updated to:

Li Yan, MD, PhD
VP, Head Unit Physician

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information

Previous Text

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Site Address and email address
Primary Medical Monitor	PPD MD	PPD	PPD	GlaxoSmithKline 1250 South Collegeville Road, UP4410 Collegeville, PA 19426, USA PPD

Revised Text

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Site Address and email address
Primary Medical Monitor	PPD MD	PPD	PPD	GlaxoSmithKline 1250 South Collegeville Road, UP4410 Collegeville, PA 19426, USA PPD

Section 1 Protocol Synopsis for Study 201973:

Objective(s)/Endpoint(s)

Rationale: The objectives/endpoints section in synopsis was modified so that evaluation of ESR1 mutational status was captured as an exploratory endpoint and not a secondary endpoint.

Phase I

Previous text:

Objectives	Endpoints
Secondary	
• To evaluate the clinical activity of GSK525762 and fulvestrant, when given in combination in women with advanced or metastatic ER+BC	• Disease control rate (DCR; defined as CR plus PR plus stable disease [SD] rate), duration of response, and progression-free survival (PFS), Time to progression (TTP)
• To characterize the exposure to GSK525762 and fulvestrant, when given in combination.	• Concentrations of GSK525762, GSK525762 relevant metabolites and fulvestrant following administration in combination
• 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 ER+BC	• Targeted sequencing of tumor tissue to determine correlation between ESR1 mutations and clinical response
Exploratory	
• 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

Revised text:

Objectives	Endpoints
Secondary	
• To evaluate the clinical activity of GSK525762 and fulvestrant, when given in combination in women with advanced or metastatic ER+BC	• Disease control rate (DCR; defined as CR plus PR plus stable disease [SD] rate), duration of response, and progression-free survival (PFS)~~, Time to progression (TTP)~~
• To characterize the exposure ~~-~~to GSK525762 and fulvestrant, when given in combination.	• Concentrations of GSK525762, GSK525762 relevant metabolites and fulvestrant following administration in combination
~~• 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 ER+BC~~	~~• Targeted sequencing of tumor tissue to determine correlation between ESR1 mutations and clinical response~~
Exploratory	
• 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
	• **Targeted sequencing to determine correlation between ESR1 mutations and clinical response**
• **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**	

Objectives	Endpoints
metastatic ER+BC	

Phase II

Previous Text

Objectives	Endpoints
Secondary	
• To evaluate the effect of treatment with GSK525762 and fulvestrant, when given in combination in women with advanced or metastatic ER+BC, on additional metrics of subject survival	• Overall survival (OS), time to progression (TTP)
• To evaluate the clinical activity of GSK525762 and fulvestrant, when given in combination	• ORR, DCR
• To characterize the exposure to GSK525762, when given in combination with fulvestrant.	• GSK525762 and metabolites concentrations following administration in combination with fulvestrant
• To characterize the exposure to fulvestrant when given alone or with GSK525762	• Fulvestrant concentrations following administration alone or in combination with GSK525762
• 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 ER+BC	• Targeted sequencing of tumor tissue to determine correlation between ESR1 mutations and clinical response
Exploratory	
• 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, Cmin, Cmax), and safety/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

Revised text:

Objectives	Endpoints
Secondary	
• To evaluate the effect of treatment with GSK525762 and fulvestrant, when given in combination in women with advanced or metastatic ER+BC, on additional metrics of subject survival	• Overall survival (OS)~~, time to progression (TTP)~~
• To evaluate the clinical activity of GSK525762 and fulvestrant, when given in combination	• ORR, DCR
• To characterize the exposure to GSK525762, when	• GSK525762 and metabolites concentrations

Objectives	Endpoints
given in combination with fulvestrant.	following administration in combination with fulvestrant
• To characterize the exposure to fulvestrant when given alone or with GSK525762 • ~~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 ER+BC~~	• Fulvestrant concentrations following administration alone or in combination with GSK525762 • ~~Targeted sequencing of tumor tissue to determine correlation between ESR1 mutations and clinical response~~
Exploratory	
• To evaluate the exposure response relationship between GSK525762 and/or fulvestrant exposure and safety and efficacy parameters • To evaluate the effect of GSK525762 and fulvestrant, when given in combination, on symptoms and quality of life • **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 ER+BC**	• Relationship between GSK525762 and/or fulvestrant exposure markers (e.g. dose, Cmin, Cmax), and safety/efficacy parameters. • Change from baseline in EORTC-QLQ-C30 and EORTC-QLQ-BR23 questionnaires • **Targeted sequencing to determine correlation between ESR1 mutations and clinical response**

Overall Design

Phase I, 3rd paragraph

Rationale: The enrolment management was clarified.

Previous Text

Subjects in DL2 will begin dosing with fulvestrant at the approved dose, plus GSK525762 at the single agent RP2D. Subjects will be enrolled into one of two possible cohorts, based on their prior treatment history, as defined above. A sentinel group (comprising subjects enrolled in both cohorts) of at least 3 and up to 10 subjects will be evaluated for safety. If the DLT rate of the DL2 sentinel group does not exceed the maximum permitted toxicity rate, then up to 35 subjects will be enrolled into each cohort. If both DL1 and DL2 are open to enrollment, then subjects will be randomized 1:1 to either DL1 or DL2 until one or the other dose level is filled or terminated. All subjects would then be enrolled at the remaining dose level.

Each prior treatment history cohort (two per DL) may enroll up to 35 evaluable subjects (including subjects from the sentinel cohorts), for a total of approximately 70 subjects enrolled at each DL.

Revised text:
Subjects in DL2 will begin dosing with fulvestrant at the approved dose, plus GSK525762 at the single agent RP2D. Subjects will be enrolled into one of two possible cohorts, based on their prior treatment history, as defined above. A sentinel group (comprising subjects enrolled in both cohorts) of at least 3 and up to 10 subjects will be evaluated for safety. **During enrolment of the DL2 sentinel group, the enrolment for DL1 will be temporarily closed. After completing the enrolment for the sentinel group of DL2, the enrolment for DL1 will be re-opened and the enrolment for DL2 will be temporarily closed while waiting for the 28 days DLT observation period to be completed for all subjects.**

If the DLT rate of the DL2 sentinel group does not exceed the maximum permitted toxicity rate, ~~then up to 35 subjects will be enrolled into each cohort. If~~**enrolment for DL2 will be re-opened and the enrolment for DL1 will be temporarily closed until DL2 enrols the same number of subjects as DL1. After that,** both DL1 and DL2 ~~are~~**will be** open to enrollment, ~~then~~**and** subjects will be ~~randomized~~**assigned** 1:1 to either DL1 or DL2 until one or the other dose level is filled or terminated. All subjects would then be enrolled at the remaining dose level.

Each prior treatment history cohort (two per DL) may enroll up to 35 ~~evaluable~~ subjects (including subjects from the sentinel cohorts), for a total of approximately 70 subjects enrolled at each DL.

Section 1 Protocol Synopsis for Study 201973: Analysis (2nd paragraph)

Rationale: The synopsis was updated to clarify enrollment for interim analysis.

Previous Text

The first interim analysis in each cohort will be performed once 10 evaluable subjects have enrolled in that cohort. Enrollment to an individual cohort may be stopped early for toxicity or lack of efficacy, but cohorts will not be stopped early if the ORR meets or exceeds the alternate hypothesis at the interim analyses.

Revised text

The first interim analysis in each cohort will be performed ~~once~~ **when at least** 10 evaluable subjects have enrolled in that cohort. Enrollment to an individual cohort may be stopped early for toxicity or lack of efficacy, but cohorts will not be stopped early if the ORR meets or exceeds the alternate hypothesis at the interim analyses.

Section 3 OBJECTIVE(S) AND ENDPOINT(S)

Rationale: The objectives/endpoints section was modified so that evaluation of ESR1 mutational status was captured as an exploratory endpoint and not a secondary endpoint.

Phase I

Previous text:

Objectives	Endpoints
Secondary	
• To evaluate the clinical activity of GSK525762 and fulvestrant, when given in combination in women with advanced or metastatic ER+BC	• Disease control rate (DCR; defined as CR plus PR plus stable disease [SD] rate), duration of response, and progression-free survival (PFS), Time to progression (TTP)
• To characterize the exposure to GSK525762 and fulvestrant, when given in combination.	• Concentrations of GSK525762, GSK525762 relevant metabolites and fulvestrant following administration in combination
• 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 ER+BC	• Targeted sequencing of tumor tissue to determine correlation between ESR1 mutations and clinical response
Exploratory	
• 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

Revised text:

Objectives	Endpoints
Secondary	
• To evaluate the clinical activity of GSK525762 and fulvestrant, when given in combination in women with advanced or metastatic ER+BC	• Disease control rate (DCR; defined as CR plus PR plus stable disease [SD] rate), duration of response, and progression-free survival (PFS)~~, Time to progression (TTP)~~
• To characterize the exposure to GSK525762 and fulvestrant, when given in combination.	• Concentrations of GSK525762, GSK525762 relevant metabolites and fulvestrant following administration in combination
~~• 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 ER+BC~~	~~• Targeted sequencing of tumor tissue to determine correlation between ESR1 mutations and clinical response~~
Exploratory	
• 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
	• **Targeted sequencing to determine correlation between ESR1 mutations and clinical response**
• **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**	

Objectives	Endpoints
metastatic ER+BC	

Phase II

Previous Text

Objectives	Endpoints
Secondary	
• To evaluate the effect of treatment with GSK525762 and fulvestrant, when given in combination in women with advanced or metastatic ER+BC, on additional metrics of subject survival	• Overall survival (OS), time to progression (TTP)
• To evaluate the clinical activity of GSK525762 and fulvestrant, when given in combination	• ORR, DCR
• To characterize the exposure to GSK525762, when given in combination with fulvestrant.	• GSK525762 and metabolites concentrations following administration in combination with fulvestrant
• To characterize the exposure to fulvestrant when given alone or with GSK525762	• Fulvestrant concentrations following administration alone or in combination with GSK525762
• 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 ER+BC	• Targeted sequencing of tumor tissue to determine correlation between ESR1 mutations and clinical response
Exploratory	
• 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, Cmin, Cmax), and safety/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

Revised text:

Objectives	Endpoints
Secondary	
• To evaluate the effect of treatment with GSK525762 and fulvestrant, when given in combination in women with advanced or metastatic ER+BC, on additional metrics of subject survival	• Overall survival (OS)~~, time to progression (TTP)~~
• To evaluate the clinical activity of GSK525762 and fulvestrant, when given in combination	• ORR, DCR
• To characterize the exposure to GSK525762, when given in combination with fulvestrant.	• GSK525762 and metabolites concentrations following administration in combination with

Objectives	Endpoints
	fulvestrant
• To characterize the exposure to fulvestrant when given alone or with GSK525762 • ~~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 ER+BC~~	• Fulvestrant concentrations following administration alone or in combination with GSK525762 • ~~Targeted sequencing of tumor tissue to determine correlation between ESR1 mutations and clinical response~~
Exploratory	
• To evaluate the exposure response relationship between GSK525762 and/or fulvestrant exposure and safety and efficacy parameters • To evaluate the effect of GSK525762 and fulvestrant, when given in combination, on symptoms and quality of life • **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 ER+BC**	• Relationship between GSK525762 and/or fulvestrant exposure markers (e.g. dose, Cmin, Cmax), and safety/efficacy parameters. • Change from baseline in EORTC-QLQ-C30 and EORTC-QLQ-BR23 questionnaires • **Targeted sequencing to determine correlation between ESR1 mutations and clinical response**

Section 4.1 Overall Design: Phase I

Rationale: The enrolment management was clarified.

Previous Text

Subjects in DL2 will begin dosing with fulvestrant at the approved dose, plus GSK525762 at 80 mg once daily. Subjects will be enrolled into one of two possible cohorts, based on their prior treatment history, as defined above. A sentinel group of at least 3 and up to 10 subjects will be evaluated for safety. If the DLT rate of the DL2 sentinel group does not exceed the maximum permitted toxicity rate as defined by the mTPI, then up to 35 subjects will be enrolled into each cohort. If both DL1 and DL2 are open to enrollment, then subjects will be randomized 1:1 to either DL1 or DL2 until one or the other dose level is filled or terminated. All subjects would then be enrolled at the remaining dose level. Refer to Section 4.2.3.2 for details of dose level and cohort selection.

Each cohort (two at each DL) may enroll up to 35 evaluable subjects, for a total of approximately 70 subjects enrolled at each DL.

Revised Text

Subjects in DL2 will begin dosing with fulvestrant at the approved dose, plus GSK525762 **at the single agent RP2D**~~at 80 mg once daily~~. Subjects will be enrolled

into one of two possible cohorts, based on their prior treatment history, as defined above. A sentinel group **(comprising subjects enrolled in both cohorts)** of at least 3 and up to 10 subjects will be evaluated for safety. **During enrolment of the DL2 sentinel group, the enrolment for DL1 will be temporarily closed. After completing the enrolment for the sentinel group of DL2, the enrolment for DL1 will be re-opened and the enrolment for DL2 will be temporarily closed while waiting for the 28 days DLT observation period to be completed for all subjects.**

If the DLT rate of the DL2 sentinel group does not exceed the maximum permitted toxicity rate**, enrolment for DL2 will be re-opened and the enrolment for DL1 will be temporarily closed until DL2 enrols the same number of subjects as DL1. After that, both DL1 and DL2 will be open to enrollment, and subjects will be assigned 1:1 to either DL1 or DL2 until one or the other dose level is filled or terminated.**~~as defined by the mTPI, then up to 35 subjects will be enrolled into each cohort. If both DL1 and DL2 are open to enrollment, then subjects will be randomized 1:1 to either DL1 or DL2 until one or the other dose level is filled or terminated.~~ All subjects would then be enrolled at the remaining dose level. Refer to Section 4.2.3.2 for details of dose level and cohort selection.

Each cohort (two at each DL) may enroll up to 35 ~~evaluable~~ subjects, for a total of approximately 70 subjects enrolled at each DL.

Section 4.2 Phase I

Rationale: The term evaluable was removed for alignment with the statistical analysis plan.

Previous Text

Each cohort (two at each DL) may enroll up to 35 evaluable subjects, for a total of approximately 70 subjects enrolled at each dose level.

Revised Text

Each cohort (two at each DL) may enroll up to 35 ~~evaluable~~ subjects, for a total of approximately 70 subjects enrolled at each dose level.

Section 4.2.3.2 Dose Level & Cohort Selection

Rationale: The enrolment management was clarified

Previous Text.

If DL2 is found to be safe in this sentinel group, enrollment will continue simultaneously into both DL1 and DL2. Any eligible subject will be randomized 1:1 to either DL1 or DL2 until the cohort at either dose level is full or closed early for toxicity or lack of efficacy. Once the randomization starts, the toxicity (DLT rate) will be monitored using Bayesian logistic regression model (BLRM).

Revised Text

If DL2 is found to be safe in this sentinel group, enrollment will **be prioritized to DL2 until it enrols the same numbers of subjects as DL1**~~continue simultaneously into both DL1 and DL2~~. A**fter that, a**ny eligible subject will be ~~randomized~~ **assigned** 1:1 to either DL1 or DL2 until the cohort at either dose level is full or closed early for toxicity or lack of efficacy.~~ Once the randomization starts, the toxicity (DLT rate) will be monitored using Bayesian logistic regression model (BLRM).~~

Section 4.2.3.3 Dose Escalation & Cohort Safety Decisions, 1st paragraph

Rationale: The Dose Escalation Plan was added per an update to GSK written standards.

Previous Text.

A data review team, consisting (at a minimum) of the investigator(s), Medical Monitors, safety physician, pharmacokineticist, clinical representatives, and statistician will be responsible for determining whether dose escalation and expansion during Phase I should continue as planned according to the mTPI design rules together with the predicted DLT rates at all DLs. Prior to the dose escalation decision, the data review team will review available relevant data on all AEs including non-DLT toxicities, laboratory assessments and other safety evaluations, as well as any available PK data. The dose decision and rationale for each cohort will be documented in writing with copies maintained at each study site and in the master study files at GlaxoSmithKline (GSK).

Revised Text

A data review team, consisting (at a minimum) of the investigator(s), Medical Monitors, safety physician, pharmacokineticist, clinical representatives, and statistician will be responsible for determining whether dose escalation and expansion during Phase I should continue as planned according to the mTPI design rules together with the predicted DLT rates at all DLs. Prior to the dose escalation decision, the data review team will review available relevant data on all AEs including non-DLT toxicities, laboratory assessments and other safety evaluations, as well as any available PK data **as described in the Dose Escalation Plan. Quality control of critical safety data will also be described in the Dose Escalation Plan, which includes ongoing study monitoring visits, Sponsor review of the clinical database, and confirmation by site investigators and/or delegate that the data is accurate and complete. The dose-escalation decision and rationale for each cohort will be discussed with investigators during teleconference(s).** The dose decision and rationale for each cohort will be documented in writing with copies maintained at each study site and in the master study files at GlaxoSmithKline (GSK).

Section 4.2.5.1 Safety Analysis

Rationale: The term evaluable was removed for alignment with the statistical analysis plan.

Previous Text

At each safety interim analysis, the number of DLTs, number of evaluable subjects, and the observed DLT rate will be reported for each cohort. The mTPI decision rule will be used for monitoring safety until 35 evaluable subjects have been assigned at the same dose, at which time further enrollment will halt.

Revised Text

At each safety interim analysis, the number of DLTs, number of evaluable subjects, and the observed DLT rate will be reported for each cohort. The mTPI decision rule will be used for monitoring safety until 35 ~~evaluable~~ subjects have been assigned at the same dose, at which time further enrollment will halt.

Section 4.2.5.2 Futility Analysis

Rationale: The term posterior was removed for alignment with the statistical analysis plan.

Previous Text

When at least 10 evaluable subjects are available in a cohort, the first interim data review on efficacy may take place for that expansion cohort. After that, interim analysis may be conducted after every 5 evaluable subjects become available. For each cohort, the enrollment for that cohort may be stopped due to futility if the Bayesian posterior probability that the confirmed response rate ≥25% (target) is small (e.g., less than a 10% chance). For details, please see Section 9.4.

Revised Text

When at least 10 evaluable subjects are available in a cohort, the first interim data review on efficacy may take place for that expansion cohort. After that, interim analysis may be conducted after every 5 evaluable subjects become available. For each cohort, the enrollment for that cohort may be stopped due to futility if the Bayesian ~~posterior~~ **predictive** probability that the confirmed response rate ≥25% (target) is small (e.g., less than a 10% chance). For details, please see Section 9.4.

Section 4.3 Decision to Proceed to Phase II

Rationale: These sections were updated to clarify the determination of RP2D and beginning of Part II.

Previous Text

Phase I will be considered complete when a RP2D has been established. The decision to proceed to Phase II will be based on totally of data including safety, efficacy, PK and PD data.

At the completion of Phase I, any subjects still receiving therapy with GSK525762 and fulvestrant may continue receiving drug(s) until progression, death, withdrawal of consent, or unacceptable toxicity, as described in Section 5.4.

Revised Text

~~Phase I will be considered complete when a RP2D has been established.~~ The decision to proceed to Phase II will be based on ~~totally~~ **totality** of data including safety, efficacy, PK and PD data.

~~At the completion of Phase I~~**After RP2D is established**, any subjects still receiving therapy with GSK525762 and fulvestrant may continue receiving drug(s) until progression, death, withdrawal of consent, or unacceptable toxicity, as described in Section 5.4.

Section 4.5.1 Phase I, 3rd paragraph

Rationale: These sections were updated for alignment with the statistical analysis plan.

Previous Text

Dose escalation/de-escalation decisions will be based primarily on the mTPI design [Ji, 2010], a well-validated method for identifying the MTD of oncology therapeutics. To facilitate dose escalation/de-escalation decisions, a Bayesian logistic regression model (BLRM) may be utilized to predict the probability of DLT at the DLs yet to be tested. Specifically, a 4 parameter BLRM for combination treatment will be fitted on the dose limiting toxicity data (i.e., absence or presence of DLT) accumulated throughout the dose-escalation to model the dose-toxicity relationship of GSK525762 and fulvestrant when given in combination [Gasparini, 2009]. This model will take into account all available data at all dose levels. Dose re-escalation after a de-escalation step may be permitted based on the results of the model and of the mTPI decision rules.

Revised Text

Dose escalation/de-escalation decisions will be based primarily on the mTPI design [Ji, 2010], a well-validated method for identifying the MTD of oncology therapeutics. ~~To facilitate dose escalation/de-escalation decisions, a Bayesian logistic regression model (BLRM) may be utilized to predict the probability of DLT at the DLs yet to be tested. Specifically, a 4 parameter BLRM for combination treatment will be fitted on the dose limiting toxicity data (i.e., absence or presence of DLT) accumulated throughout the dose-escalation to model the dose-toxicity relationship of GSK525762 and fulvestrant when given in combination [Gasparini, 2009]. This model will take into account all available data at all dose levels. Dose re-escalation after a de-escalation step may be permitted based on the results of the model and of the mTPI decision rules.~~

Section 5.1 Inclusion Criteria

Table 2 Definitions for Adequate Organ Function

Rationale: Either troponin I or T may be used for determination of troponin levels.

Previous Text

Cardiac	
Ejection fraction	≥ LLN by echocardiogram or MUGA scan
Troponin (T)	≤ ULN

Revised Text

Cardiac	
Ejection fraction	≥ LLN by echocardiogram or MUGA scan
Troponin (**I or** T)	≤ ULN

Section 5.4 Withdrawal/Stopping Criteria, 11th paragraph

Rationale: The study completion criteria were modified for clarity.

Previous Text

In Phase II, unless a disease cohort is closed early, survival follow-up will continue in each cohort until approximately 70% of the total number of subjects have progressed or died. At such time, the cohort will be closed and any further follow-up on subjects enrolled in that cohort will cease.

Revised Text

In Phase II, unless a disease cohort is closed early, survival follow-up will continue in each cohort until approximately 70% of the total number of subjects have ~~progressed or~~ died At such time, **the study will be considered completed** ~~the cohort will be closed~~ and any further follow-up on subjects enrolled ~~in that cohort~~ will cease.

Section 5.5 Subject and Study Completion, 2nd paragraph

Rationale: The study completion criteria were modified for clarity.

Previous Text

Subjects who have not died, and are no longer being followed for survival are considered to have discontinued the study. The End of Study electronic Case Record Form (eCRF) should only be completed when a subject is no longer being followed. Phase 1 of the study can be considered completed for purpose of a final Part 1 analysis if 70% of the subjects have progressed or died. The study will be considered completed for purposes of a final analysis when approximately 70% of subjects enrolled in Phase II have progressed or died.

Revised Text

Subjects who have not died, and are no longer being followed for survival are considered to have discontinued the study. The End of Study electronic Case Record Form (eCRF) should only be completed when a subject is no longer being followed. ~~Phase 1 of the study can be considered completed for purpose of a final Part 1 analysis if 70% of the subjects have progressed or died.~~ The study will be considered completed **for purposes of final analysis when approximately 70% of the subjects enrolled in Phase II have died. However, the study could be stopped due to toxicity or futility before that when there is enough evidence to conclude as such.**~~for purposes of a final analysis when approximately 70% of subjects enrolled in Phase II have progressed or died.~~

Section 6.2.1 Phase I, 4th paragraph

Rationale: The enrolment management guidelines were modified for clarity.

Previous Text

Once DL2 has been cleared in dose escalation, subjects will be enrolled into the prior treatment-specific cohorts at either DL1 or DL2 provided that:

- There are remaining slots in the cohort
- Either cohort has not closed due to unacceptable toxicity or lack of efficacy

Revised Text

Once DL2 has been cleared in dose escalation, **enrolment will be prioritized to DL2 until it enrols the same number of subjects as DL1. After that** subjects will be enrolled into the prior treatment-specific cohorts at either DL1 or DL2 provided that:

- There are remaining slots in the cohort
- Either cohort has not closed due to unacceptable toxicity or lack of efficacy

Section 6.6 Preparation/Handling/Storage/Accountability, 2nd paragpraph

Rationale: The additional precautions for drug handling were included for safety.

Previous Text

- Further guidance and information for final disposition of unused study treatment are provided in the SRM.

Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

Revised Text

- Further guidance and information for final disposition of unused study treatment are provided in the SRM.

Limited exposure and precautionary action (example: wearing gloves, washing hands post exposure, etc.) should be taken by site staff dispensing GSK525762 tablets.

~~Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.~~ A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

Section 6.11.2.3 Cautionary Medications, 6th paragraph, new text added

Rationale: Information was added pertaining to concomitant medications that are substrates of CYP3A4.

Previous Text

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

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

Revised Text

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

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

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

Section 7.2 Screening and Critical Baseline Assessments

Rationale: Clinical baseline assessments were modified to better accommodate screening patients for eligibility criteria.

Previous Text

Screening procedures should be performed as rapidly as possible within 14 days prior to Day 1 (first dose of study medication) to facilitate subject entry requirements. In case of abnormal test values, retesting may be performed if medically indicated and within 14 days prior to Day 1.

Revised Text

Screening procedures should be performed as rapidly as possible within ~~14~~ **28** days prior to Day 1 (first dose of study medication) to facilitate subject entry requirements. **Clinical lab assessments should be completed within 14 days prior to dosing and i**~~I~~n case of abnormal test values, retesting may be performed if medically indicated and within 14 days prior to Day 1.

Section 7.2 Screening and Critical Baseline Assessments

Rationale: Clinical baseline assessments were modified to better accommodate screening patients for eligibility criteria.

Previous Text

Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging studies, etc.) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed 14 days prior to Day 1 (first dose of study medication) unless otherwise indicated: CT scans (within 30 days prior to Day 1) and ECHO/MUGA (within 35 days prior to Day 1).

Revised Text

Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging studies, etc.) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed **28**~~1~~4 days prior to Day 1 (first dose of study medication) unless otherwise indicated: CT scans (within 30 days prior to Day 1) and ECHO/MUGA (within 35 days prior to Day 1).

Section 7.2.1 Critical Baseline Assessments

Rationale: Clinical baseline assessments were modified to better accommodate screening patients for eligibility criteria.

Previous Text

- Phase I:

- All subjects must provide a biopsy sample at screening. Archival tissue is permitted; however, if no archival tissue is available then a fresh biopsy specimen must be provided.
- At least 6 subjects at each dose level will be required to provide paired fresh biopsies pre- and post-dose at the time points indicated in Section 7.1, as described in Section 7.5.1. Fresh biopsies should be paired with plasma samples for PK, collected as close as possible to the biopsy (ideally within 1 h). Subjects will be informed at the time of informed consent whether paired fresh biopsies will be required. Further details regarding sample type and processing will be provided in the SRM.

Revised Text

- Phase I:
  - All subjects must provide a biopsy sample at screening. Archival tissue is permitted; however, if no archival tissue is available then a fresh biopsy specimen must be provided **within 14 days prior to first study dose**.
  - At least 6 subjects at each dose level will be required to provide paired fresh biopsies pre- and post-dose at the time points indicated in Section 7.1, as described in Section 7.5.1. Fresh biopsies should be paired with plasma samples for PK, collected as close as possible to the biopsy (ideally within 1 h). **Subjects should have at least four consecutive doses of GSK525762 prior to collection of tumor biopsy, whether they have had a dose interruption or not.** Subjects will be informed at the time of informed consent whether paired fresh biopsies will be required. Further details regarding sample type and processing will be provided in the SRM.

Section 7.2.2 Visit Windows

Rationale: The visit windows were updated to better accommodate visit assessments.

Previous Text

Screening (baseline to pre-dose): Screening echocardiogram or MUGA scan should be completed within 35 days prior to the first dose of study drugs. Baseline imaging should be completed within 30 days prior to the first dose of study drug. All other assessments should be completed within 14 days prior to first dose of study drugs. Clinical labs performed during screening within 72 hours of first dose do not need to be repeated on Day 1.

Revised Text

Screening (baseline to pre-dose): Screening echocardiogram or MUGA scan should be completed within 35 days prior to the first dose of study drugs. Baseline imaging should be completed within 30 days prior to the first dose of study drug. **Clinical lab**

assessments should ~~All other assessments should~~ be completed within 14 days prior to first dose of study drugs. Clinical labs performed during screening within 72 hours of first dose do not need to be repeated on Day 1. **All other assessments should be completed with 28 days prior to first dose of study drug.**

Section 7.2.2 Visit Windows

Rationale: The visit windows were updated to better accommodate visit assessments.

Previous Text

Weeks 4, 5, and 9: Clinic visits may be scheduled ± 3 days. The first disease assessment (at Week 9) may be scheduled ± 7 days.

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

Every 4-week and 8-week visits after Week 49: Every 4-week visits (and their associated laboratory studies) are no longer required, based on clinical judgment. Every 8-week clinic visits can be scheduled ± 7 days.

Revised Text

Weeks 4, 5, and 9: Clinic visits may be scheduled ± 3 days. The first disease assessment (at Week 9) may be scheduled ± 7 days.

Weeks 6, 7, 8, and 11: Lab visits may be scheduled ± 3 days.

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

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

Section 7.3.4 Clinical Safety Laboratory Assessments

Table 10 Clinical Laboratory Tests

Rationale: The laboratory assessments were clarified for BUN values and bilirubin assessments.

Previous Text

Clinical Chemistry	
Sodium	Fasting Glucose
Potassium	Magnesium
Chloride	Calcium (total and ionized)
Total Carbon Dioxide	Total Protein
Blood Urea Nitrogen	Albumin
Creatinine	
Liver Function	
Bilirubin (Total and Direct)	
Aspartate Aminotransferase	
Alanine Aminotransferase	
Alkaline Phosphatase	
Cardiac Studies	
Troponin (I or T at local laboratory)	
NT-proBNP	
Fasting Lipid panel (Total Cholesterol, LDL, HDL, triglycerides)	

Note: Not all studies are performed at each visit; please refer to Section 7.1, Table 7 and Table 9 for timing of required studies

Revised Text

Clinical Chemistry	
Sodium	Fasting Glucose
Potassium	Magnesium
Chloride	Calcium (total and ionized)
Total Carbon Dioxide	Total Protein
Blood Urea Nitrogen*****	Albumin
Creatinine	
Liver Function	
Bilirubin (Total and Direct)******	
Aspartate Aminotransferase	
Alanine Aminotransferase	
Alkaline Phosphatase	
Cardiac Studies	
Troponin (I or T~~ at local laboratory~~)	
NT-proBNP	
Fasting Lipid panel (Total Cholesterol, LDL, HDL, triglycerides)	

***Direct and/or calculated BUN values are acceptable.**

****Direct Bilirubin is only required if total bilirubin values are abnormal.**

Note: Not all studies are performed at each visit; please refer to Section 7.1, Table 7 and Table 9 for timing of required studies

Section 7.3.5.3 Follow-up of AEs and SAEs

Rationale: All AEs are followed until resolution.

Previous Text

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest

(as defined in Appendix 10) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 10.

Revised Text

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs ~~of special interest~~ (as defined in Appendix 10) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 10.

Section 7.5.1 Tumor Biopsy Collection/Surgical Procedures

Rationale: Clarification was added to the collection of biopsies

Previous Text

In Phase I, paired fresh biopsies must be provided pre- (within 14 days of the first dose) and on-treatment at the time points indicated for at least 6 subjects (out of 35 planned for enrollment) at each dose level.

Revised Text

In Phase I, paired fresh biopsies must be provided pre- (within 14 days ~~of~~ **prior to** the first dose) and on-treatment at the time points indicated for at least 6 subjects (out of 35 planned for enrollment) at each dose level.

Section 7.7.1 Tumor Biomarker Analysis

Rationale: The methods performed for exploratory analysis were updated and clarified.

Previous Text

Evaluation of ESR1 mutation status will be performed, using a pre-treatment biopsy sample (archival tissue or a recent biopsy) on all tumors.

To further characterize the subject population, DNA, RNA and/or protein measurements may be utilized to identify predictors of sensitivity or resistance to GSK525762 and fulvestrant in combination utilizing baseline tissue (archival tissue or a recent biopsy) and tissue obtained at disease progression (if sample is available).

Revised Text

~~Evaluation of ESR1 mutation status will be performed, using a pre-treatment biopsy sample (archival tissue or a recent biopsy) on all tumors.~~

To further characterize the subject population, DNA, RNA and/or protein measurements may be utilized to identify predictors of sensitivity or resistance to GSK525762 and fulvestrant in combination utilizing baseline tissue (archival tissue or a recent biopsy) and tissue obtained at disease progression (if sample is available).

Section 7.7.3 Circulating cell free DNA/RNA Analysis (New subsection added)

Rationale: The methods performed for exploratory analysis were updated and clarified.

Revised Text

Plasma isolated from blood collected at screening will be used to evaluate ESR1mutation status in circulating cell-free deoxyribonucleic (cfDNA) and/or RNA.

To further characterize the subject population, cfDNA and/or RNA measurements may be utilized to identify predictors of sensitivity or resistance to GSK525762 and fulvestrant in combination utilizing plasma isolated from blood at screening, on treatment and/or end of treatment.

Section 9.1.2 Phase I Efficacy

Rationale: The statistical methodology and terminology for efficacy analysis was corrected and clarified.

Previous Text

Phase I portion of the study will employ a Bayesian predictive adaptive design [Lee, 2008] that allows the trial to be monitored more frequently at multiple stages. The criteria will be based on a historically unimportant ORR of 10% versus an ORR of interest of 25%. Bayesian statistics will be employed to calculate the posterior probability that the RR ≥25% and ≥10% at interim assuming a Beta prior for the Binomial distributed data. Predictive probability calculates the probability that the RR ≥25% or ≥10% given the responses have already been observed.

Revised Text

Phase I portion of the study will employ a Bayesian predictive adaptive design [Lee, 2008] that allows the trial to be monitored more frequently at multiple stages. The criteria will be based on a historically unimportant ORR of 10% versus an ORR of interest of 25%. Bayesian statistics will be employed to calculate the ~~posterior~~ **predictive** probability that the RR ≥25% and ≥10% at interim assuming a Beta prior for the Binomial distributed data. Predictive probability calculates the probability that the RR ≥25% or ≥10% given the responses have already been observed.

Section 9.1.2 Phase I Efficacy

Rationale: The term posterior was removed for alignment with the statistical analysis plan and other corrections noted.

Previous Text

For the separate interim looks in each cohort, the enrollment for that cohort may be stopped due to futility if the posterior probability that the confirmed RR ≥25% is small (e.g., less than a 4% chance for a total sample size of 35 subjects). Enrollment 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 less than 1 confirmed responses are observed in the first 14 evaluable subjects. The evaluable subject is defined as a subject, who has either progressed, withdrew from the study, was lost to follow-up, or is ongoing and has completed at least one post treatment disease assessment. For example, when there are 14 evaluable subjects available at the time of interim analysis with only one response, then the cohort may be stop for futility. Otherwise, the enrollment of the respective cohort will continue to the target sample size.

Revised Text

For the separate interim looks in each cohort, the enrollment for that cohort may be stopped due to futility if the ~~posterior~~ **predictive** probability that the confirmed RR ≥25% is small (e.g., less than a 4% chance for a total sample size of 35 subjects). Enrollment 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 less than 1 confirmed responses are observed in the first 14 evaluable subjects. The evaluable subject is defined as a subject, who has either progressed **or died**, withdrew from the study **treatment**, ~~was lost to follow-up,~~ or is ongoing and has completed at least ~~one~~ **two** post treatment disease assessment**s**. For example, when there are 14 evaluable subjects available at the time of interim analysis with only one response, then the cohort may be stop for futility. Otherwise, the enrollment of the respective cohort will continue to the target sample size.

Section 9.3.1 Analysis Populations

Rationale: The definition of evaluable subjects was updated.

Previous Text

All Evaluable Subjects will be defined as the study population used for decision-making at the interim futility analysis. Subjects who have at least two post-baseline radiological disease assessments and have been on study for at least 49 days or have progressed or died or permanently withdraw from the study will be included in this population.

Revised Text

All Evaluable Subjects will be defined as the study population used for decision-making at the interim futility analysis. Subjects who have at least two post-baseline radiological disease assessments ~~and have been on study for at least 49 days~~ or have progressed or died or permanently withdraw from the study **treatment** will be included in this population.

Section 9.3.2.1.1 Dose Escalation and Safety Analyses

Rationale: The statistical methodology for mTPI was described elsewhere in the protocol.

Previous Text

Once 3-10 subjects have been enrolled at each dose level, an interim analysis will be performed to determine if dose-escalation and/or dose expansion is appropriate. The primary driver for the dose escalation/expansion decisions in Phase I will be safety and tolerability of each dose cohort.

To facilitate dose escalation/de-escalation decisions, a Bayesian logistic regression model (BLRM) may be utilized to predict the probability of DLT at the dose levels yet to be tested. Specifically, a 4-parameter BLRM for combination treatment will be fitted on the dose limiting toxicity data (i.e., absence or presence of DLT) accumulated throughout the dose-escalation to model the dose-toxicity relationship of GSK525762 and fulvestrant when given in combination. Prior distributions of two parameters for GSK525762 will be calculated based on the toxicity data observed in the FTIH study where GSK525762 is administered alone; similarly, prior distributions of two parameters for fulvestrant will be determined based on data observed in the FTIH study where fulvestrant is administered alone; a non-informative prior will be assumed for the parameter which accounts for the combination of two compounds. Further details regarding such analyses will be provided in the RAP.

Revised Text

Once 3-10 subjects have been enrolled at each dose level, an interim analysis will be performed to determine if dose-escalation and/or dose expansion is appropriate. The primary driver for the dose escalation/expansion decisions in Phase I will be safety and tolerability of each dose cohort.

~~To facilitate dose escalation/de-escalation decisions, a Bayesian logistic regression model (BLRM) may be utilized to predict the probability of DLT at the dose levels yet to be tested. Specifically, a 4-parameter BLRM for combination treatment will be fitted on the dose limiting toxicity data (i.e., absence or presence of DLT) accumulated throughout the dose-escalation to model the dose-toxicity relationship of GSK525762 and fulvestrant when given in combination. Prior distributions of two parameters for GSK525762 will be calculated based on the toxicity data observed in the FTIH study where GSK525762 is administered alone; similarly, prior distributions of two parameters for fulvestrant will be determined based on data observed in the FTIH study where fulvestrant is administered alone; a non-informative prior will be assumed for the parameter which accounts for the combination of two compounds. Further details regarding such analyses will be provided in the RAP.~~

Section 9.3.2.1.2 Efficacy Analyses

Rationale: The statistical methodology and terminology for efficacy analyses was corrected and clarified.

Previous Text

Interim analyses during expansion cohorts

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

The study population used for decision-making at the interim analyses on efficacy will be termed All Evaluable Subjects. This will be the population for Bayesian model and summaries of response if data warrant. Because subjects enroll at different times, not all subjects will have been on the study long enough to have single or multiple disease assessments. Since disease assessments are to be completed every 8 weeks, subjects who have at least two post-baseline radiological disease assessments and have been on study for at least 49 days or have progressed or died or permanently withdraw from the study will be included in this population. Interim analysis on safety will be conducted on all treated subjects.

Revised Text

Interim analyses during expansion cohorts

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. Enrollment may be stopped early in any of the expansion cohorts for toxicity or lack of efficacy, should various criteria occur based on accrued data. The decision criteria for early stop for futility based on Bayesian Hierarchical model are described below. The decision will be made for each individual prior treatment history-specific cohort.

The study population used for decision-making at the interim analyses on efficacy will be termed All Evaluable Subjects. This will be the population for Bayesian model and summaries of response if data warrant. Because subjects enroll at different times, not all subjects will have been on the study long enough to have single or multiple disease assessments. Since disease assessments are to be completed every 8 weeks, subjects who have at least two post-baseline radiological disease assessments ~~and have been on study for at least 49 days~~ or have progressed or died or permanently withdraw from the study **treatment** will be included in this population. Interim analysis on safety will be conducted on all treated subjects.

Section 9.4.8.1 Phase I

Rationale: The term posterior was removed for alignment with the statistical analysis plan.

Previous Text

The observed confirmed and unconfirmed ORR will be reported at the interim and final analysis for each cohort specified in Phase 1 treated dose, if data warrant. The estimates along with 95% exact confidence interval (CI) will be provided. Bayesian inference based on summary statistics from the posterior distributions of each ORR will be reported at interim and final analyses. The posterior mean and posterior 2.5% and 97.5% percentiles of the ORR will be calculated for each cohort. In addition, the posterior probability that the ORR exceeds its corresponding historical control will be reported for each cohort.

Revised Text

The observed confirmed and unconfirmed ORR will be reported at the interim and final analysis for each cohort specified in Phase 1 treated dose, if data warrant. The estimates along with 95% exact confidence interval (CI) will be provided. Bayesian inference based on summary statistics from the posterior distributions of each ORR will be reported at interim and final analyses. The posterior mean and posterior 2.5% and 97.5% percentiles of the ORR will be calculated for each cohort. In addition, the ~~posterior~~ **predictive** probability that the ORR exceeds its corresponding historical control will be reported for each cohort.

Section 9.4.10.6 Mean Proportion of advancing to Phase 2

Rationale: The statistical methodology and terminology for safety and efficacy analyses were corrected and/or clarified.

Previous Text

To evaluate the design performance in making the decision of advancing to Phase 2, Table 12 listed the probabilities of advancing any or both of the two doses to Phase 2 after Phase 1. In the scenario where both DLs are safe and positive, there is a 92.4% chance that at least one dose will be picked for Phase 2. If the trial data indicates both doses are safe and positive, the utility function calculation discussed in Section 9.1.2 will be used as guidance to pick the best dose to take into Phase 2. When both dose levels are safe but not positive, there is 16% chance that at least one dose will be picked for Phase II.

Revised Text

To evaluate the design performance in making the decision of advancing to Phase 2, Table 12 listed the probabilities of advancing any or both of the two doses to Phase 2 after Phase 1. In the scenario where both DLs are safe and positive, there is a 92.4% chance that at least one dose will be picked for Phase 2. ~~If the trial data indicates both doses are safe and positive, the utility function calculation discussed in Section 9.1.2 will be used as guidance to pick the best dose to take into Phase 2.~~ When both dose levels are safe but not positive, there is 16% chance that at least one dose will be picked for Phase II.

Section 10.3 Quality Control (Study Monitoring)

Rationale: The text was clarified as PAREXEL monitors will perform the monitoring visits.

Previous Text

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.

Revised Text

- In accordance with applicable regulations including GCP, and GSK procedures, ~~GSK~~ monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.

Section 12.2 Appendix 2: Management of Suspected Toxicity Table 13 Dose Adjustment/Stopping Safety Criteria

Rationale: The cardiac management guidelines were updated in response to the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM).

Previous Text

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

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
	minutes)	This subject may consider restarting study treatment at a one dose level reduced if all of the following criteria for QTcF re-challenge are met. If approval for re-challenge is granted, the subject must be re-consented (with a separate informed consent specific to QTc prolongation) (1) QTcF reduced to <450 msec, (2) Potassium and magnesium levels are within institutional normal range, (3) A favorable risk/benefit profile (in the medical judgement of the Investigator and the Medical Monitor), (4) Approval within GSK medical governance: a. agreement with SERM MD and PPL, b. review with Chair or co-Chair of the GSK QT panel, c. SERM VP and Clinical VP approval d. Head Unit Physician approval (5) Institutional IRB (or equivalent) approval, and (6) The subject is re-consented regarding the possible increased risk of QTc prolongation. • Discontinuation procedures: If the subject is withdrawn due to QTcF event, the subject should complete the following activities post-dose: (1) Evaluation by cardiologist. (2) Weekly assessments for QTcF should be performed for two weeks, and then next assessment at 4 weeks post-dose. (3) If QTcF results have not resolved to baseline by 4 weeks post-dose, then continue every 4-5 weeks until resolution
	• Elevated bilirubin, hypoalbuminemia, prolonged PT, ascites, and/or encephalopathy	Refer to Appendix 13 for definition of Child-Pugh score • Child-Pugh Class A: No change to fulvestrant dose required • Child-Pugh Class B: Reduce dose of fulvestrant to 250 mg, administered as per the standard schedule. Fulvestrant dose may be re-escalated to 500 mg once liver function improves. • Child-Pugh Class C: Hold fulvestrant until liver function has improved In addition, please refer to "other non-hematologic toxicity", below, for management of GSK525762
	• Elevated bilirubin without other evidence of liver injury	Refer to "other non-hematologic toxicity", below

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Hypo- and Hyperglycemia (for management purposes, refer to mild, moderate and severe intensity criteria; however for CRF reporting use NCI-CTCAE v4.0 [NCI, 2009] grading system)	• Fasting blood glucose >150 mg/dL to 250 mg/dL (Mild hyperglycemia)	• Monitor fasting and preprandial glucose. • If persistant over 2 repeats over 3-4 weeks, consult Diabetologist, consider starting metformin
	• Fasting blood glucose any blood glucose >250 mg/dL (Moderate to Severe hyperglycemia)	• Hold investigational product(s) and instruct subject to notify investigator immediately. • Monitor for ketoacidosis as clinically indicated. • If subject has evidence of ketoacidosis, initiate prompt therapy. Antihyperglycemic therapy with insulin is preferred. Consult Diabetologist/Endocrinologist .Careful monitoring should be performed to control for rebound hypoglycemia as effect of investigational product(s) resolve • May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with Medical Monitor.
Diarrhea	• Grade 1	• Initiate supportive care including loperamide.
	• Grade 2	• Initiate supportive care including loperamide. Consider temporary discontinuation of study medications and discuss with Medical Monitor.

Revised Text

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
QTcF	If >30msec and < 60 msec change from baseline AND manual QTcF <500 (average of three ECGs over at least 15 minutes)	Continue current dose of GSK525762 • **Evaluation by cardiologist** • Supplement electrolytes, particularly potassium and magnesium, to recommended levels: c. Maintain serum potassium > 4mol/L d. Maintain serum magnesium levels >0.85 mmol/L • Discontinue any concomitant medications with potential for QTcF prolongation. • Consider 24 hour or longer telemetry monitoring if clinically indicated.
	If ≥ 60 msec change from baseline occurs OR QTcF ≥500 (average of three ECGs over at least 15 minutes)	Discontinue GSK525762 and notify the Medical Monitor. • **Evaluation by cardiologist** • Supplement electrolytes to recommended levels: c. Maintain serum potassium > 4mol/L d. Maintain serum magnesium levels >0.85 mmol/L • Rule out other potential etiologies for prolonged QTcF such as cardiac ischemia • Discontinue any concomitant medications with potential for QTcF prolongation. • ~~Consider~~ **24-hour** telemetry monitoring if clinically indicated. This subject may consider restarting study treatment at a one dose level reduced if all of the following criteria for QTcF re-challenge are met. If approval for re-challenge is granted, the subject must be re-consented (with a separate informed consent specific to QTc prolongation) (1) QTcF reduced to <450 msec, (2) Potassium and magnesium levels are within institutional normal range, (3) A favorable risk/benefit profile (in the medical judgement of the Investigator and the Medical Monitor), (4) Approval within GSK medical governance: a. agreement with SERM MD and PPL, b. review with Chair or co-Chair of the GSK QT panel, c. SERM VP and Clinical VP approval d. Head Unit Physician approval ~~(5) Institutional IRB (or equivalent) approval, and~~ (5) The subject is re-consented regarding the possible increased risk of QTc prolongation. • Discontinuation procedures: If the subject is withdrawn due to QTcF event, the subject should complete the following activities post-dose: (1) Evaluation by cardiologist. (2) Weekly assessments for QTcF **until ≤30 msec change from baseline reached** ~~should be~~

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
		~~performed for two weeks~~, and then next assessment at 4 weeks post-dose. (3) If QTcF results have not resolved to baseline by 4 weeks post-dose, then continue every 4-5 weeks until resolution

Section 12.7.1 Baseline Documentation of Target and Non-Target Lesions

Rationale: The baseline assessment was modified to accommodate patient visit schedules.

Previous Text

- All baseline lesion assessments must be performed within 14 days of randomization.

Revised Text

- All baseline lesion assessments must be performed within ~~14~~ **28** days of randomization.

Section 12.10.2 Definition of Serious Adverse Events

Rationale: The terminology "events of special interest" was removed to clarify that all SAEs are followed until resolution.

Previous Text

g. Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

h. Protocol-specific SAEs (events of special interest):

LVEF decreases (Section 5.4.3) meeting stopping criteria

Liver chemistry abnormalities meeting stopping criteria (Section 5.4.1) QTcF prolongation meeting stopping criteria (Section 5.4.2) New primary cancers
• Refer to Appendix 8 for the required liver chemistry follow-up instructions

Revised Text

g. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.
~~**h. Protocol-specific SAEs (events of special interest):**~~ ~~LVEF decreases (Section 5.4.3) meeting stopping criteria~~ ~~Liver chemistry abnormalities meeting stopping criteria (Section 5.4.1)~~ ~~QTcF prolongation meeting stopping criteria (Section 5.4.2)~~ ~~New primary cancers~~
• Refer to Appendix 8 for the required liver chemistry follow-up instructions

Section 7

Rationale: The Times and Events tables in Section 7.1 was updated to clarify ECHO/MUGA scan requirements for screening and W1D1, timing of on treatment biopsy collection in Ph I, lab assessment requirements, and length of screening window (also updated throughout the document).

Table 16 Time and Events, Phase I

Previous Text

Procedure	SCR	Week 1		Week 2		Week 3		Week 4	Week 5	q4w	q8w	q8w	EOT[1]
		D1	D4	D1	D4	D1	D4	D1	D1	W9 to W49	W9 to W49	W49 and thereafter	
Screening[2]													
Informed Consent	X												
Demography	X												
Medical History	X												
Inclusion/Exclusion Criteria	X												
Disease Characteristics	X												
Prior Therapy[3]	X												
Register Subject	X												
Safety													
Physical Exam[4]	X	X		X		X		X	X	X			X
ECOG PS	X	X		X		X		X	X	X			X
12-lead ECGs (Triplicate)[5]	X	X	X	X		X		X	X	X			X
Clinical Laboratory Assessments[6]	X	X	X	X	X	X	X	X	X	X			X
Echocardiogram or MUGA[7]	X	X							X	Week 13, 25, 37, 49			X
PRO-CTCAE[8]	X	X		X		X		X	X	X		X	X
Study Treatment													
Administer GSK525762[9]		Daily											
Administer Fulvestrant[9]		X				X			X	X			
AE/SAE review		Continuous from signing of informed consent											
Concomitant medication review		Continuous from signing of informed consent											

Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)													
PK blood samples[10]		PK				PK			O		X		
Tumor biopsy[11]	X					One sample, collected between W3D1 and W4D1, as close as possible to 3-6h post-GSK525762 dose							X[12]
Whole blood for exploratory analyses	X							X					X
PGx blood sample		X											
Efficacy													
CT chest/abdomen/pelvis[13]	X										X	X	X
EORTC-QLQ-C30 & EORTC-QLQ-BR23[14]	X	X		X		X		X	X	X		X	X

1. Applies to subjects who withdraw for any reason prior to progression or who progress during study treatment. Following this visit, subjects will be contacted approximately every 3 months (± 14 days) to collect: survival status as of last date of contact and initiation of new anti-cancer therapy. Contact may be completed via a clinic visit, a telephone contact or an email.
2. Screening procedures should be performed as rapidly as possible within 14 days prior to Day 1 (first dose of study medication) to facilitate subject entry requirements. In case of abnormal test values, retesting may be performed if medically indicated and within 14 days prior to Day 1. Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging studies, etc.) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within 14 days prior to Day 1 (first dose of study medication) unless otherwise indicated: CT scans (within 30 days prior to Day 1) and ECHO/MUGA (within 35 days prior to Day 1).
3. Including dates of imaging and sizes of target lesion(s) used for RECIST 1.1 evaluation, if available.
4. Complete physical examination required at screening, Week (W)1 Day (D)1 (W1D1), and end of the treatment (EOT) visits. Limited examinations permitted at all other visits, as noted. Definition of complete and limited examinations may be found in Section 7.3.1.
5. Triplicate ECGs should be performed prior to dosing and evaluated for abnormality prior to administration of dose.
6. Refer to Table 7 for details of clinical safety labs and timing of collection
7. Whatever scanning modality is used at screening should be maintained for all subsequent scans. Beginning at W13, scans will be performed once every 12 weeks.
8. Patient Reported Outcomes Version of the Common a Terminology Criteria for Adverse Events (PRO-CTCAE) Item Library (Version 1.0). Post Week 49, assessments will be completed every 8 weeks.
9. Drugs should be administered as described in Section 6.1. Visits where fulvestrant is administered will be considered drug dispensing days. There is a ±3 day window for fulvestrant dosing. On PK collection days in Week 1 and Week 3, subjects should abstain from food from 8 h prior until 2 h after dose as described in Section 6.10.1. Post Week 49, fulvestrant will continue to be administered every 4 weeks. Refer to the SRM for further details.
10. "PK" = serial PK days. Sample collections should be obtained at the following timepoints: Pre-dose, 30 m ± 5 m, 1 h ± 10 m, 3 h ± 30 m. "O" = sample collections to be obtained pre-dose, 0.5-1h post-dose, and an optional sample 4-8h post-dose. "X" = sample collections to be obtained pre-dose as well as 0.5-1h post-dose (note that routine PK is no longer required once the subject has been on study for 26 weeks). Pre-dose samples will be split to obtain a PK sample for fulvestrant analysis. Refer to the SRM for further details.
11. Screening (archival) tumor biopsy specimen required for all subjects; if archival sample is not available then fresh specimen must be provided as described in Section 7.7.2. Paired fresh biopsies must be provided pre- and on-treatment at the time points indicated for at least 6 subjects (out of 35 planned for enrollment) at each dose level. Subjects providing an on-treatment fresh tumor biopsy must have received at least 4 consecutive doses of GSK525762 prior to the collection of the tissue. If the post-dose biopsy is not performed during this timeframe due to lab abnormalities or subject status, it should be performed at the next agreed upon visit with the medical monitor after subject recovery. A limited number of additional subjects may be requested to provide pre and on-treatment biopsies based on emerging data. Fresh biopsies should be paired with plasma samples for PK, collected as close as possible to biopsy (ideally within 1 h). Subjects must have a platelet count of ≥75,000/mm^3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy, or any other planned surgical procedure.Refer to the SRM for further details.
12. A tumor biopsy at the end of treatment is optional.
13. CT should be performed with oral and intravenous (IV) contrast. CT required at screening. Any potential CR or PR should be confirmed as described in Appendix 7. EOT disease assessment is not required if reason for discontinuing therapy was progressive disease and prior assessment was within 14 days of EOT visit. Subjects with contraindication to contrast-enhanced computed tomography (CT) may have other imaging performed as described in Section 7.2.1.
14. European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core-30 and Breast 23 measures. Post Week 49, assessments will be completed every 8 weeks.

Revised Text

Procedure	SCR	Week 1		Week 2		Week 3		Week 4	Week 5	q4w	q8w	q8w	q12w	EOT[1]
		D1	D4	D1	D4	D1	D4	D1	D1	W9 to W49	W9 to W49	W49 and thereafter	W49 and thereafter	
Screening[2]														
Informed Consent	X													
Demography	X													
Medical History	X													
Inclusion/Exclusion Criteria	X													
Disease Characteristics	X													
Prior Therapy[3]	X													
Register Subject	X													
Safety														
Physical Exam[4]	X	X		X		X		X	X	X			**X**	X
ECOG PS[5]	X	X		X		X		X	X	X			**X**	X
12-lead ECGs (Triplicate)[6~~5~~]	X	X	X	X		X		X	X	X			**X**	X
Clinical Laboratory Assessments[7~~6~~]	X	X	X	X	X	X	X	X	X	X				X
Echocardiogram or MUGA[8~~7~~]	X	~~X~~							X	Week 13, 25, 37, 49			**X**	X
PRO-CTCAE[9~~8~~]	X	X		X		X		X	X	X		X		X
Study Treatment														
Administer GSK525762[10~~9~~]		Daily												
Administer Fulvestrant[10~~9~~]		X				X			X	X				
AE/SAE review		Continuous from signing of informed consent												
Concomitant medication review		Continuous from signing of informed consent												

Procedure	SCR	Week 1		Week 2		Week 3		Week 4	Week 5	q4w	q8w	q8w	q12w	EOT[1]
		D1	D4	D1	D4	D1	D4	D1	D1	W9 to W49	W9 to W49	W49 and thereafter	W49 and thereafter	
Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)														
PK blood samples[11~~10~~]		PK				PK			O		X			
Tumor biopsy[12~~11~~]	X					One sample, collected between W3D**4**~~1~~ and W**5**4D1, as close as possible to 3-6h post-GSK525762 dose								X[13~~12~~]
Whole blood for exploratory analyses	X							X						X
PGx blood sample		X												
Efficacy														
CT chest/abdomen/pelvis[14~~13~~]	X										X	X		X
EORTC-QLQ-C30 & EORTC-QLQ-BR23[15~~14~~]	X	X		X		X		X	X	X		X		X

1. Applies to subjects who withdraw for any reason prior to progression or who progress during study treatment. Following this visit, subjects will be contacted approximately every 3 months (± 14 days) to collect: survival status as of last date of contact and initiation of new anti-cancer therapy. Contact may be completed via a clinic visit, a telephone contact or an email.
2. Screening procedures should be performed as rapidly as possible within **28 days** ~~14 days~~ prior to Day 1 (first dose of study medication) to facilitate subject entry requirements. **Clinical lab assessments should be completed within 14 days prior to dosing, and i**~~I~~n case of abnormal test values, retesting may be performed if medically indicated and within 14 days prior to Day 1. Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging studies, etc.) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within ~~14~~ **28** days prior to Day 1 (first dose of study medication) unless otherwise indicated: CT scans (within 30 days prior to Day 1) and ECHO/MUGA (within 35 days prior to Day 1).
3. Including dates of imaging and sizes of target lesion(s) used for RECIST 1.1 evaluation, if available.
4. Complete physical examination required at screening, Week (W)1 Day (D)1 (W1D1), and end of the treatment (EOT) visits. Limited examinations permitted at all other visits, as noted. Definition of complete and limited examinations may be found in Section 7.3.1. **Post Week 49, assessments will be completed every 12 weeks.**
5. **Post Week 49, ECOG assessments will be completed every 12 weeks.**
6. Triplicate ECGs should be performed prior to dosing and evaluated for abnormality prior to administration of dose. **Post Week 49, assessments will be completed every 12 weeks.**
7. Refer to Table 7 for details of clinical safety labs and timing of collection
8. Whatever scanning modality is used at screening should be maintained for all subsequent scans. Beginning at W13, scans will be performed once every 12 weeks.
9. Patient Reported Outcomes Version of the Common a Terminology Criteria for Adverse Events (PRO-CTCAE) Item Library (Version 1.0). Post Week 49, assessments will be completed every 8 weeks.
10. Drugs should be administered as described in Section 6.1. Visits where fulvestrant is administered will be considered drug dispensing days. There is a ±3 day window for fulvestrant dosing. On PK collection days in Week 1 and Week 3, subjects should abstain from food from 8 h prior until 2 h after dose as described in Section 6.10.1. Post Week 49, fulvestrant will continue to be administered every 4 weeks. Refer to the SRM for further details.

11. "PK" = serial PK days. Sample collections should be obtained at the following timepoints: Pre-dose, 30 m ± 5 m, 1 h ± 10 m, 3 h ± 30 m. "O" = sample collections to be obtained pre-dose, 0.5-1h post-dose, and an optional sample 4-8h post-dose. "X" = sample collections to be obtained pre-dose as well as 0.5-1h post-dose (note that routine PK is no longer required once the subject has been on study for 26 weeks). Pre-dose samples will be split to obtain a PK sample for fulvestrant analysis. Refer to the SRM for further details.
12. Screening (archival) tumor biopsy specimen required for all subjects; if archival sample is not available then fresh specimen must be provided **within 14 days prior to first study dose** as described in Section 7.7.2. Paired fresh biopsies must be provided pre- and on-treatment at the time points indicated for at least 6 subjects (out of 35 planned for enrollment) at each dose level. Subjects providing an on-treatment fresh tumor biopsy**, whether they have had a dose interruption of GSK525762 or not,** must have received at least 4 consecutive doses of GSK525762 prior to the collection of the tissue. If the post-dose biopsy is not performed during this timeframe due to lab abnormalities or subject status, it should be performed at the next agreed upon visit with the medical monitor after subject recovery. A limited number of additional subjects may be requested to provide pre and on-treatment biopsies based on emerging data. Fresh biopsies should be paired with plasma samples for PK, collected as close as possible to biopsy (ideally within 1 h). Subjects must have a platelet count of ≥75,000/mm^3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy, or any other planned surgical procedure.Refer to the SRM for further details.
13. A tumor biopsy at the end of treatment is optional**, but strongly encouraged when clinically feasible**.
14. CT should be performed with oral and intravenous (IV) contrast. CT required at screening. Any potential CR or PR should be confirmed as described in Appendix 7. EOT disease assessment is not required if reason for discontinuing therapy was progressive disease and prior assessment was within 14 days of EOT visit. Subjects with contraindication to contrast-enhanced computed tomography (CT) **or MRI** may have ~~other~~ imaging performed as described in Section 7.2.1.
15. European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core-30 and Breast 23 measures. Post Week 49, assessments will be completed every 8 weeks.

Section 7 Table 7 Time and Events, Phase I Laboratory Assessments

Previous Text

	SCR	Week 1		Week 2		Week 3		Week 4	Week 5	Week 7	Week 9	Week 11	q4w	EOT
		D1	D4	D1	D4	D1	D4	D1	D1	D1	D1	D1	W13 and thereafter	
Clinical chemistry	X	X	X	X		X		X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Troponin, N-terminal pro–B-Type natriuretic peptide (NT- proBNP)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation	X	X	X	X		X		X	X	X	X	X	X	X
Factor VII Assay[1]	X					X			X					
Fasting blood glucose	X	X	X	X		X		X	X	X	X	X	X	X
HbA1c	X								X	X	X	X	X	X
Fasting lipids	X								X	X	X	X	X	X
Thyroid (Thyroid stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4))	X								X	X	X	X	X	X
Pancreatic	X	X		X		X		X	X	X	X	X	X	X
Urinalysis	X	X		X		X		X	X	X	X	X	X	X
HIV, Hepatitis B surface antigen (HBsAg), Hepatitis C Virus (HCV) Antibody	X													
FSH/Estradiol[2]	X													
Pregnancy test[3]	X	X				X			X	X	X	X	X	X

1. Also perform if PT or INR are ≥1.5XULN, or in case of bleeding event
2. Only required at screening for pre- and peri-menopausal subjects
3. Serum pregnancy test within 7 days prior to first dose; urine or serum test thereafter

Revised Text

	SCR[1]	Week 1		Week 2		Week 3		Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 11	q4w	Q12w	EOT
		D1	D4	D1	D4	D1	D4	D1	D1	D1	D1	D1	D1	D1	W13 and thereafter	W49 and thereafter	
Clinical chemistry	X	X	X	X		X		X	X		X		X	X	X	**X**	X
Hematology	X	X	X	X	X	X	X	X	X		X		X	X	X	**X**	X
Liver chemistry	X	X	X	X	X	X	X	X	X	**X**	X	**X**	X	X	X		X
Troponin, N-terminal pro–B-Type natriuretic peptide (NT-proBNP)	X	X	X	X	X	X	X	X	X		X		X	X	X	**X**	X
Coagulation	X	X	X	X		X		X	X		X		X	X	X	**X**	X
Factor VII Assay[2]	X					X			X								
Fasting blood glucose	X	X	X	X		X		X	X		X		X	X	X	**X**	X
HbA1c	X								X		X		X	X	X	**X**	X
Fasting lipids	X								X		X		X	X	X	**X**	X
Thyroid (Thyroid stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4))[3]	X								X		X		X	X	X	**X**	X
Pancreatic	X	X		X		X		X	X		X		X	X	X	**X**	X
Urinalysis	X	X		X		X		X	X		X		X	X	X	**X**	X

	SCR[1]	Week 1		Week 2		Week 3		Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 11	q4w	Q12w	EOT
		D1	D4	D1	D4	D1	D4	D1	D1	D1	D1	D1	D1	D1	W13 and thereafter	W49 and thereafter	
HIV, Hepatitis B surface antigen (HBsAg), Hepatitis C Virus (HCV) Antibody	X																
FSH/Estradiol[42]	X																
Pregnancy test[53]	X	X				X			X		X		X	X	X	**X**	X

1. Although strongly preferred, lab results for HBA1c, fasting lipids, TSH/T3/T4, and pancreatic enzymes are not required prior to dosing.

2. Also perform if PT or INR are ≥1.5XULN, or in case of bleeding event

3. TSH testing is mandatory. T4 testing is only required if TSH is abnormal. T3 testing is required when clinically applicable (if both TSH and T4 are abnormal).

4. Only required at screening for pre- and peri-menopausal subjects

5. Serum pregnancy test within 7 days prior to first dose; urine or serum test thereafter

Section 7 Table 17 Time and Events, Phase II

Previous Text

Procedure	SCR	Week 1		Week 2	Week 3	Week 4	Week 5	q4w	q8w	q8w	EOT[1]
		D1	D4	D1	D1	D1	D1	W9 to W49	W9 to W49	W49 and thereafter	
Screening[2]											
Informed Consent	X										
Demography	X										

Medical History	X										
Inclusion/Exclusion Criteria	X										
Disease Characteristics	X										
Prior Therapy[3]	X										
Register Subject	X										
Safety											
Physical Exam[4]	X	X		X	X	X	X	X			X
ECOG PS	X	X		X	X	X	X	X			X
12-lead ECGs (Triplicate)[5]	X	X	X	X	X	X	X	X			X
Clinical Laboratory Assessments[6]	X	X	X	X	X	X	X	X			X
Echocardiogram or MUGA[7]	X	X					X	Week 13, 25, 37, 49			X
PRO-CTCAE[8]	X	X		X	X	X	X	X		X	X
Study Treatment											
Administer GSK525762[9]		Daily									
Administer Fulvestrant[9]		X			X		X	X			
AE/SAE review		Continuous from signing of informed consent									
Concomitant medication review		Continuous from signing of informed consent									
Pharmacokinetics (PK), Translational Studies & Pharmacogenomics (PGx)											
PK blood samples[10]		O					O		X		
Tumor biopsy (archival)[11]	X										X[12]
Whole blood for exploratory analyses	X					X					X
PGx blood sample		X									
Efficacy											
CT chest/abdomen/pelvis[13]	X								X	X	X
EORTC-QLQ-C30 & EORTC-QLQ-BR23[14]	X	X		X	X	X	X	X		X	X

1. Applies to subjects who withdraw for any reason prior to progression or who progress during study treatment. Following this visit, subjects will be contacted approximately every 3 months (± 14 days) to collect: survival status as of last date of contact and initiation of new anti-cancer therapy. Contact may be completed via a clinic visit, a telephone contact or an email.
2. Screening procedures should be performed as rapidly as possible within 14 days prior to Day 1 (first dose of study medication) to facilitate subject entry requirements. In case of abnormal test values, retesting may be performed if medically indicated and within 14 days prior to Day 1. Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging studies, etc.) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within 14 days prior to Day 1 (first dose of study medication) unless otherwise indicated: CT scans (within 30 days prior to Day 1) and ECHO/MUGA (within 35 days prior to Day 1).
3. Including dates of imaging and sizes of target lesion(s) used for RECIST 1.1 evaluation, if available.
4. Complete physical examination required at screening, Week (W)1 Day (D)1 (W1D1), and end of the treatment (EOT) visits. Limited examinations permitted at all other visits, as noted. Definition of complete and limited examinations may be found in Section 7.3.1.
5. Triplicate ECGs should be performed prior to dosing and evaluated for abnormality prior to administration of dose.
6. Refer to Table 9 for details of clinical safety labs and timing of collection
7. Whatever scanning modality is used at screening should be maintained for all subsequent scans. Beginning at W13, scans will be performed once every 12 weeks.
8. Patient Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Item Library (Version 1.0). Post Week 49, assessments will be completed every 8 weeks.
9. Drugs should be administered as described in Section 6.1. Visits where fulvestrant is administered will be considered drug dispensing days. There is a ±3 day window for the fulvestrant dosing. Post Week 49, fulvestrant will continue to be administered every 4 weeks. Refer to the SRM for further details.
10. "O" = sample collections to be obtained pre-dose, 0.5-1h post-dose, and an optional sample 4-8h post-dose. "X" = sample collections to be obtained pre-dose as well as 0.5-1h post-dose (note that routine PK is no longer required once the subject has been on study for 26 weeks). Pre-dose samples will be split to obtain a PK sample for fulvestrant analysis only for subjects who are receiving fulvestrant. Refer to the SRM for further details.
11. Screening (archival) tumor biopsy specimen required for all subjects; if archival sample is not available then fresh specimen must be provided. Refer to Section 7.2.1 and to the SRM for further details. Subjects must have a platelet count of ≥75,000/mm3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy, or any other planned surgical procedure.
12. Tumor biopsy at the end of treatment is optional.
13. CT should be performed with oral and intravenous (IV) contrast. Any potential CR or PR should be confirmed as described in Appendix 7. EOT disease assessment is not required if reason for discontinuing therapy was progressive disease and prior assessment was within 14 days of EOT visit. Subjects with contraindication to contrast-enhanced computed tomography (CT) may have other imaging performed as described in Section 7.2.1.
14. European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core-30 and Breast 23 measures. Post Week 49, assessments will be completed every 8 weeks.

Revised Text

Procedure	SCR	Week 1		Week 2	Week 3	Week 4	Week 5	q4w	q8w	q8w	q12w	EOT[1]
		D1	D4	D1	D1	D1	D1	W9 to W49	W9 to W49	W49 and thereafter	W49 and thereafter	
Screening[2]												
Informed Consent	X											
Demography	X											
Medical History	X											
Inclusion/Exclusion Criteria	X											
Disease Characteristics	X											
Prior Therapy[3]	X											
Register Subject	X											
Safety												
Physical Exam[4]	X	X		X	X	X	X	X			**X**	X
ECOG PS[5]	X	X		X	X	X	X	X			**X**	X
12-lead ECGs (Triplicate)[6~~5~~]	X	X	X	X	X	X	X	X			**X**	X
Clinical Laboratory Assessments[7~~6~~]	X	X	X	X	X	X	X	X				X
Echocardiogram or MUGA[8~~7~~]	X	~~X~~					X	Week 13, 25, 37, 49			**X**	X
PRO-CTCAE[9~~8~~]	X	X		X	X	X	X	X		X		X
Study Treatment												
Administer GSK525762[10~~9~~]		Daily										
Administer Fulvestrant[10~~9~~]		X			X		X	X				
AE/SAE review			Continuous from signing of informed consent									
Concomitant medication review			Continuous from signing of informed consent									
Pharmacokinetics (PK), Translational Studies & Pharmacogenomics (PGx)												
PK blood samples[11~~10~~]		O					O		X			
Tumor biopsy (archival)[12~~11~~]	X											X[13~~12~~]
Whole blood for exploratory analyses	X					X						X
PGx blood sample		X										
Efficacy												

CT chest/abdomen/pelvis[14~~13~~]	X								X	X		X
EORTC-QLQ-C30 & EORTC-QLQ-BR23[15~~14~~]	X	X		X	X	X	X	X		X		X

1. Applies to subjects who withdraw for any reason prior to progression or who progress during study treatment. Following this visit, subjects will be contacted approximately every 3 months (± 14 days) to collect: survival status as of last date of contact and initiation of new anti-cancer therapy. Contact may be completed via a clinic visit, a telephone contact or an email.
2. Screening procedures should be performed as rapidly as possible within ~~14~~**28** days prior to Day 1 (first dose of study medication) to facilitate subject entry requirements. **Clinical lab assessments should be completed within 14 days prior to dosing, and in** ~~In~~ case of abnormal test values, retesting may be performed if medically indicated and within 14 days prior to Day 1. Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging studies, etc.) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within ~~14~~**28** days prior to Day 1 (first dose of study medication) unless otherwise indicated: CT scans (within 30 days prior to Day 1) and ECHO/MUGA (within 35 days prior to Day 1).
3. Including dates of imaging and sizes of target lesion(s) used for RECIST 1.1 evaluation, if available.
4. Complete physical examination required at screening, Week (W)1 Day (D)1 (W1D1), and end of the treatment (EOT) visits. Limited examinations permitted at all other visits, as noted. Definition of complete and limited examinations may be found in Section 7.3.1. **Post Week 49, assessments will be completed every 12 weeks.**
5. **Post Week 49, ECOG assessments will be completed every 12 weeks.**
6. Triplicate ECGs should be performed prior to dosing and evaluated for abnormality prior to administration of dose. **Post Week 49, assessments will be completed every 12 weeks.**
7. Refer to Table 9 for details of clinical safety labs and timing of collection
8. Whatever scanning modality is used at screening should be maintained for all subsequent scans. Beginning at W13, scans will be performed once every 12 weeks.
9. Patient Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Item Library (Version 1.0). Post Week 49, assessments will be completed every 8 weeks.
10. Drugs should be administered as described in Section 6.1**.** Visits where fulvestrant is administered will be considered drug dispensing days. There is a ±3 day window for the fulvestrant dosing. Post Week 49, fulvestrant will continue to be administered every 4 weeks. Refer to the SRM for further details.
11. "O" = sample collections to be obtained pre-dose, 0.5-1h post-dose, and an optional sample 4-8h post-dose. "X" = sample collections to be obtained pre-dose as well as 0.5-1h post-dose (note that routine PK is no longer required once the subject has been on study for 26 weeks). Pre-dose samples will be split to obtain a PK sample for fulvestrant analysis only for subjects who are receiving fulvestrant. Refer to the SRM for further details.
12. Screening (archival) tumor biopsy specimen required for all subjects; if archival sample is not available then fresh specimen must be provided **within 14 days prior to first study dose**. Refer to Section 7.2.1 and to the SRM for further details. Subjects must have a platelet count of ≥75,000/mm3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy, or any other planned surgical procedure.
13. Tumor biopsy at the end of treatment is optional**, but strongly encouraged when clinically feasible**.
14. CT should be performed with oral and intravenous (IV) contrast. Any potential CR or PR should be confirmed as described in Appendix 7. EOT disease assessment is not required if reason for discontinuing therapy was progressive disease and prior assessment was within 14 days of EOT visit. Subjects with contraindication to contrast-enhanced computed tomography (CT) **or MRI** may have ~~other~~ imaging performed as described in Section 7.2.1.
15. European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core-30 and Breast 23 measures. Post Week 49, assessments will be completed every 8 weeks.

Section 7 Table 18 Time and Events, Phase 2 Laboratory Assessments

Previous Text

	SCR	Week 1		Week 2	Week 3	Week 4	Week 5	Week 7	Week 9	Week 11	q4w	EOT
		D1	D4	D1	D1	D1	D1	D1	D1	D1	W13 and thereafter	
Clinical chemistry	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X
Liver chemistry	X	X	X	X	X	X	X	X	X	X	X	X
Troponin, N-terminal pro–B-Type natriuretic peptide (NT-proBNP)	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation	X	X	X	X	X	X	X	X	X	X	X	X
Factor VII Assay[1]	X				X		X					
Fasting blood glucose	X	X	X	X	X	X	X	X	X	X	X	X
HbA1c	X						X	X	X	X	X	X
Fasting lipids	X						X	X	X	X	X	X
Thyroid (Thyroid stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4))	X						X	X	X	X	X	X
Pancreatic	X	X		X	X	X	X	X	X	X	X	X
Urinalysis	X	X		X	X	X	X	X	X	X	X	X
HIV, Hepatitis B surface antigen (HBsAg), Hepatitis C Virus (HCV) Antibody	X											
FSH/Estradiol[2]	X											
Pregnancy test[3]	X	X			X		X	X	X	X	X	X

1. Also perform if PT or INR are ≥1.5XULN, or in case of bleeding event
2. Only required at screening for pre- and peri-menopausal subjects
3. Serum pregnancy test within 7 days prior to first dose; urine or serum test thereafter

Revised Text

	SCR[1]	Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 11	q4w	q12w	EOT
		D1	D4	D1	D1	D1	D1	D1	D1	D1	D1	D1	W13 and thereafter	W49 and thereafter	
Clinical chemistry	X	X	X	X	X	X	X		X		X	X	X	**X**	X
Hematology	X	X	X	X	X	X	X		X		X	X	X	**X**	X
Liver chemistry	X	X	X	X	X	X	X	**X**	X	**X**	X	X	X		X
Troponin, N-terminal pro–B-Type natriuretic peptide (NT-proBNP)	X	X	X	X	X	X	X		X		X	X	X	**X**	X
Coagulation	X	X	X	X	X	X	X		X		X	X	X	**X**	X
Factor VII Assay[2]	X				X		X								
Fasting blood glucose	X	X	X	X	X	X	X		X		X	X	X	**X**	X
HbA1c	X						X		X		X	X	X	**X**	X
Fasting lipids	X						X		X		X	X	X	**X**	X
Thyroid (Thyroid stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4))[3]	X						X		X		X	X	X	**X**	X
Pancreatic	X	X		X	X	X	X		X		X	X	X	**X**	X
Urinalysis	X	X		X	X	X	X		X		X	X	X	**X**	X
HIV, Hepatitis B surface antigen (HBsAg), Hepatitis C Virus (HCV) Antibody	X														
FSH/Estradiol[4]	X														
Pregnancy test[5]	X	X			X		X		X		X	X	X	**X**	X

1. **Although strongly preferred, lab results for HBA1c, fasting lipids, TSH/T3/T4, and pancreatic enzymes are not required prior to dosing.**
2. Also perform if PT or INR are ≥1.5XULN, or in case of bleeding event
3. **TSH testing is mandatory. T4 testing is only required if TSH is abnormal. T3 testing is required when clinically applicable (if both TSH and T4 are abnormal).**
4. Only required at screening for pre- and peri-menopausal subjects
5. Serum pregnancy test within 7 days prior to first dose; urine or serum test thereafter

12.14.5. Amendment 05

Protocol changes for Amendment 05 (11-SEP-2018), from protocol changes to amendment 04 (18-OCT-2017)

Amendment 05 summary:

Amendment 05 applies to all global study sites.

Changes to the protocol include:
These changes are based upon revisions noted by the study team, and include:

Updating the protocol title to hormone receptor positive (HR+/HER2- BC) to align with the inclusion criteria which requires both ER+ and PR+ BC subjects.

Corrections made throughout to align HR+/HER2- BC with the inclusion criteria and title.

Update to clarify that DL 2 (80 mg) has been discontinued.

Update to the author list and sponsor signatory.

In introduction and Section 5.4 include requirement that the Medical Monitor (MM) should be consulted before a subject can discontinue one agent and continue on the other.

Study Design in Synopsis and Section 4: Original language describing Phase I and Phase II remains. New sections added to address the updates to Phase I which include DL2 (80mg) discontinuation, update the DL1 (60mg) cohort 2 population to include subjects must have received greater than or equal to 12 months of prior CDK4/6+ AI for metastatic disease and progressed while on treatment and allow bone only disease.

Revision in sub-sections of Section 4.7 to be in line with wording in the most recent Investigator's Brochure. Inclusion/exclusion criteria:

- Provision of a fresh tumor biopsy sample at screening;
- letrozole has been expanded to include all AI agents;
- prior treatment allowed in the CDK4/6 patient population;
- subjects must have received greater than or equal to 12 months of prior CDK4/6+ AI for metastatic disease and progressed while on treatment;
- bone only disease is allowed (screening biopsy not required after discussion with MM);
- update to criteria for severe or uncontrolled systemic diseases; update to criteria for baseline QTcF).

Section 5.4.2 update to QTc stopping criteria; removal of former Section 6.3.1 Guidelines for Events of Special Interest; in Section 6.11.1 include granulocyte colony-stimulating factors as a permitted medications; update to wording in Section 6.11.2.1 Prohibited Medication and removal of former Table 4; update to wording in Section 6.11.2.3 Cautionary Medication and removal of former Table 5; Clarification in Section 6.11.2.2 regarding both prescription and non-prescription herbal preparations/medications;

Time and Events Table 5 and Table 8: Updates regarding ECGs, requirement of fresh biopsies at screening and collection window, clarification of requirements around fresh tumor biopsies sample and other general clarifications; Pregnancy Test- X has been removed from the Column for Q12wks (Wk49 and after). This was an error and Q4wks is correct. In Section 7.2.2 clarification regarding PK sample collection for subjects with interrupted dosing; Section 7.3.3.1 update to guidelines for electrocardiograms assessments; update to Table 9 Clinical Labs regarding collection of troponin and adding a list of acronyms in the footnotes; update to guidance regarding screening and on treatment biopsies in Section 7.5.1 and Section 7.7.2; update to toxicity management for QTcF events in Appendix 2 and explanation for reconsent.

In Section 9.2.1.1, added the new cohort 2 based on prior experience, interim analysis and futility analysis is planned. In Section 9.4.8.1, subjects with bone only disease will be included in the final analysis

Collection of pregnancy information regarding elective termination is clarified that only those performed due to medical reasons are required to be reported.

List of Specific Changes

Text which has been added to the protocol is indicated in Appendix 12 by underlined text. Text which has been deleted from the protocol is indicated in Appendix 12 by ~~strike through~~ format.

Common amendment 1

Rationale for change: Updated to better reflect the target patient population.

REVISED TEXT

Throughout the protocol

~~ER~~HR+HER2

Common amendment 2

Rationale for change: IB version have been updated from 2011N113741_05 to 2011N113741_07.

REVISED TEXT

~~2011N113741_05~~ 2011N113741_07

Title page

Rationale for change: Updated title to better reflect the target patient population of the study.

REVISED TEXT

Title of the study

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 advanced or metastatic breast cancer (HR+/HER2-) ~~ER+~~ breast cancer

Author (s)

PPD

Sponsor Signatory

~~Li Yan~~ Michael Streit, MD ~~, PhD~~
~~VP, Head Unit Physician~~ Clinical Development Lead, Oncology

Section 1: protocol synopsis

Rationale for change: Clarification aligns with original inclusion criteria and does not reflect a change. Original language left intact and new revised section added for clarity. Closure of DL2 is based on review of interim safety and efficacy analysis and determined with agreement with investigators. DL1 cohort 1 subject enrolment is not impacted.

Addition of requirement for subjects to have ≥12 months of prior treatment is to evaluate subjects who have experienced prolonged response with this combination. Subjects with bone only disease are added to reflect 30% of metastatic breast cancer population.

REVISED TEXT

Objective(s)/Endpoint(s)

Phase I

Objectives	Endpoints
Primary	
• To determine a recommended Phase 2 dose (RP2D) of GSK525762, when given in combination with fulvestrant, in women with advanced or metastatic hormone ~~estrogen~~ receptor positive breast cancer (~~E~~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] data
Secondary	
• To determine the safety, tolerability, and maximum tolerated dose (MTD) of GSK525762, when given in combination with fulvestrant in women with advanced or metastatic ~~ER~~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 the clinical activity of GSK525762 and fulvestrant, when given in combination in women with advanced or metastatic HR+/HER2-~~ER~~ BC	• Disease control rate (DCR; defined as CR plus PR plus stable disease [SD] rate), duration of response, and progression-free survival (PFS)
Exploratory	
• To evaluate additional measures of clinical activity of GSK525762 and fulvestrant, when given in combination in women with advanced or metastatic HR+/HER2~~ER~~ BC	• Overall survival (OS)
• To identify potential indicators of sensitivity or	• ~~Transcriptomic~~ Mutational analysis~~studies~~ of tumor

Objectives	Endpoints
response to GSK525762 and fulvestrant, when given in combination in women with advanced or metastatic ER+BC.	tissue; correlation of baseline somatic and tumor-specific genetic and genomic profiles with response.
• 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- ~~ER~~ BC	• Targeted sequencing to determine correlation between ESR1 mutations and clinical response

Phase II

Objectives	Endpoints
Primary	
• To evaluate the effect of treatment with GSK525762 and fulvestrant, when given in combination, on progression-free survival in women with advanced or metastatic HR+/HER2- ~~ER~~ BC	• Progression free survival (PFS), defined as the median time from the first dose of study treatment until objective tumor progression or death from any cause, whichever comes first
Secondary	
• To evaluate the effect of treatment with GSK525762 and fulvestrant, when given in combination in women with advanced or metastatic HR+/HER2- ~~ER~~ BC, on additional metrics of subject survival	• Overall survival (OS)
Exploratory	
• To identify potential indicators of sensitivity or response to GSK525762 and fulvestrant, when given in combination in women with advanced or metastatic HR+/HER2- ~~ER~~ BC	• ~~Transcriptomic studies~~Mutational analysis of tumor tissue; correlation of baseline somatic and tumor-specific genetic and genomic profiles with response
• 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- ~~ER+~~BC	• Targeted sequencing to determine correlation between ESR1 mutations and clinical response

Overall Design

Original Overall Design (Protocols 01-04)

Phase I of the study is designed as parallel single arm treatment with GSK525762 in combination with fulvestrant in two distinct populations of ~~ER~~HR+/HER2- breast cancer to determine a recommended Phase 2 dose (RP2D) based on safety, tolerability, pharmacokinetic, and efficacy profiles. [Changes have been made to this Phase]

This cohort will compare the efficacy of GSK525762 in combination with fulvestrant versus fulvestrant with GSK525762-matched placebo in subjects with disease that progressed on anti-estrogen and/or one or more AIs, or failure of a combination treatment

with CDK4/6 inhibitor plus ~~letrozole~~ AI or a combination of both of these groups/patient populations.

Study Schematic

Phase II-Paragraph 1

Phase II is a randomized, double-blind, placebo-controlled study that will explore the clinical activity of GSK525762 and fulvestrant when given in combination, to subjects with advanced or metastatic ~~ER~~HR+/HER2- BC. The primary endpoint of Phase II is PFS. The design for Phase II will be finalized based on the results from Phase I.

Phase II-Paragraph 2

Phase II may~~will~~ enroll subjects who have disease that has progressed after prior therapy with:

- CDK4/6 inhibitor plus ~~letrozole~~AI, OR
- either AI therapy OR CDK4/6 inhibitor plus ~~letrozole~~AI. If both cohorts are permitted to enroll in Phase II, randomization will be stratified by prior CDK4/6 inhibitor-based therapy (i.e., CDK4/6 inhibitor-naïve versus CDK4/6 inhibitor-exposed) and corresponding stratified analysis will be provided at interim and final analyses.

Phase II-Paragraph 3

In addition, subjects enrolled in the CDK4/6 inhibitor plus ~~letrozole~~ AI cohort may have failed therapy with any number of lines of anti-estrogens and/or AIs.

Text added

Revised Overall Design (Protocol Amendment 05)

While the overall study goals and design remain same, changes have been made to Phase I of the study to address to emerging data and intended to better define the patient population most likely to benefit from combination treatment of molibresib plus fulvestrant. The following are to be noted:

1. DL1 Cohort 1 (60 mg, AI-failures) will complete enrolment to 35 subjects as under amendment 4

2. DL1 Cohort 2 (60 mg, CDK4/6i plus AI failure) – change in inclusion criteria and to the number of subjects to be enrolled is detailed below.

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.

4. Phase II design remains unchanged – as originally stated, this Phase of the study will be redesigned based after analysis of Phase I data.

Change to DL1 Cohort 2:

- Enrolment into DL1 (60 mg) Cohort 2 is modified. Subjects previously treated with the combination of a CDK4/6 inhibitor (e.g., palbociclib) plus letrozole AI for advanced or metastatic disease will be enrolled as follows;

    - 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.

    - 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.

    - The total number of subjects enrolled into this cohort will be approximately 75.

    - Prior ovarian suppression and/or tamoxifen are allowed as long as the other criteria are met.

This requirement is based on emerging data and intended to better define the patient population most likely to benefit from combination treatment.

Treatment and duration-Paragraph 3

Subjects who require dose reduction and/or discontinuation of one investigational agent may continue on the other agent until progression, withdrawal of consent, or unacceptable toxicity after discussion with the Medical Monitor.

Type and Number of Subjects-Paragraph 1

Approximately 294 subjects worldwide with relapsed/refractory advanced or metastatic ~~ER~~ HR+/HER2- BC will be enrolled in the study as a whole. Subjects may have disease which progressed during or within 12 months of stopping adjuvant therapy, or disease which was initially diagnosed as advanced or metastatic. Cohort 2 is modified to include a minimum of 48 subjects who have progressed after greater than or equal to 12 months of a CDK4/6 inhibitor (e.g., palbociclib) plus AI for advanced or metastatic disease with either measurable disease (32 subjects) or bone only disease (16 subjects).

Analysis-Paragraph 2

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 ~~overall~~ objective response rate (CR + PR) of 25% relative to a 10% response rate suggesting no activity. This will be conducted by testing the null hypothesis that P0<=0.1 versus the alternative that P1 >0.25, 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 the measurable disease subjects only, defined as an objective response rate (CR + PR) of 20% relative to a 5% response rate suggesting no activity. This will be conducted by testing the null hypothesis that P0<=0.05 versus the alternative that 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%.

Section 2: Introduction

Rationale for change: To align it with the population originally specified in the Inclusion and Exclusion criteria which requires both ER+ and PR+ breast cancer subjects**.**

Section 2.1: Study Rationale

REVISED TEXT

Advanced or metastatic ~~ER~~ HR+/HER2- ~~+~~BC is an incurable illness that will prove fatal for the majority of afflicted women. Current standards of care (SoC) include endocrine therapy, targeted therapy, and chemotherapy. Recent preclinical data suggest that altering the expression of the ~~ER~~HR as well as other ~~ER~~HR-responsive genes may provide therapeutic benefit for women for whom endocrine therapy alone has proven inadequate. One potential novel target for therapy is the BET family of proteins. These proteins bind to chromatin and regulate gene expression, and data suggest that combination with endocrine therapy may provide therapeutic benefit and even restore sensitivity to HR~~ER~~-targeted agents. The current protocol (201973) proposes to evaluate the combination of the BET inhibitor GSK525762 with the ER-degrading agent fulvestrant in women with metastatic or advanced ~~ER~~ HR+/HER2- BC who have progressed on at least one line of prior endocrine therapy.

Section 2.2: Brief Background

Rationale for change: As noted above.

REVISED TEXT

Paragraph 2

While patients proceed from one therapy to the next, they ultimately exhaust their options, ER HR+/HER2- BC an area of unmet need, as a result of this inexorable progression.

Paragraph 5

In the ~~ongoing~~ BET115521 monotherapy trial, ER+ breast cancer subjects with disease that progressed after multiple prior lines of therapy were enrolled. A planned interim futility analysis in this population was performed, and GSK ~~has~~ stopped enrollment in this single agent cohort, based upon limited benefit.

Paragraph 7

Taken together, these preclinical data suggest a mechanism by which BET inhibitors and endocrine-targeted therapy may combine to provide synergistic benefit in HR+/HER2 BC.

Section 3: Objective (s) and Endpoints

Rationale for change As noted above.

REVISED TEXT

Please refer to Section 1: Synopsis **-** *Objective(s)/Endpoint(s).* Same changes applies here.

Section 4.1.1: Original Overall Design (Protocols 01-04)

Rationale for change As noted above.

REVISED TEXT

4.1.1 Original Overall Design (Protocols 01-04)

Paragraph 1

Phase I of the study is designed as parallel single arm treatment with GSK525762 in combination with fulvestrant in two distinct populations of ~~ER+~~HR+/HER2- breast cancer to determine a recommended Phase 2 dose RP2D based on safety, tolerability, pharmacokinetic, and efficacy profiles. [Changes have been made to this Phase, see changes below in Section 4.1.2]

Section 4.1.2: Revised Overall Design (Protocol Amendment 05)

Rationale for change: Closure of DL2 was based on review of interim safety and efficacy analysis and determined with agreement with investigators. Addition of requirement for subjects to have ≥12 months of prior treatment is to evaluate subjects who have experienced prolonged response with this combination. Subjects with bone only disease are added to reflect 30% of metastatic breast cancer population.

REVISED TEXT

Section added

4.1.2 Revised Overall Design (Protocol Amendment 05)

While the overall study goals and design remain same, changes have been made to Phase I of the study to address to emerging data and intended to better define the patient population most likely to benefit from combination treatment of molibresib plus fulvestrant. The following are to be noted:

1. DL1 Cohort 1 (60 mg, AI-failures) will complete enrolment to 35 subjects as under amendment 4

2. DL1 Cohort 2 (60 mg, CDK4/6i plus AI failure) – change in inclusion criteria and to the number of subjects to be enrolled is detailed below in Section 4.1.2.1.

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.

4. Phase II design remains unchanged – as originally stated, this Phase of the study will be redesigned based after analysis of Phase I data.

Section 4.1.2.1: Change to DL1 Cohort 2

Rationale for change: As noted above.

REVISED TEXT

4.1.2.1 Change to DL1 Cohort 2

- 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;

    - 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.

- 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.

- The total number of subjects enrolled into this cohort will be approximately 75.

- Prior ovarian suppression and/or tamoxifen are allowed as long as the other criteria are met.

This requirement is based on emerging data and intended to better define the patient population most likely to benefit from combination treatment. The required number of subjects is described in Section 9.2.

Section 4.1.3: Type and Number of Subjects

Rationale for change: Addition of DL1 (60mg) cohort 2 population to include subjects must have received greater than or equal to 12 months of prior CDK4/6+ AI for metastatic disease and progressed while on treatment and allow bone only disease.

REVISED TEXT

Paragraph 1

All subjects enrolled in this study will have a diagnosis of advanced or metastatic ~~ER~~HR+/HER2- BC, that has progressed on prior treatment with at least one line of therapy, or which has progressed while on or within 12 months of discontinuing adjuvant endocrine therapy. Cohort 2 is modified to include a minimum of 48 subjects who have progressed after greater than or equal to 12 months of a CDK4/6 inhibitor (e.g., palbociclib) plus AI for advanced or metastatic disease with either measurable disease (32 subjects) or bone only disease (16 subjects).

Paragraph 2

Approximately 140 subjects will be enrolled in Phase I ~~(35 subjects in each of two cohorts at two DLs)~~, and approximately 154 subjects total will be enrolled in Phase II.

Section 4.2.1: Type and Number of Subjects in Phase I

Rationale for change: As noted above.

REVISED TEXT

See Protocol Section 4.1.2 for details on the type and number of subjects in Phase I.

Text deleted

~~Eligible subjects will be enrolled into one of two potential cohorts:~~

~~Subjects who have disease that has relapsed during treatment or within 12 months of completion of adjuvant therapy with an AI, OR disease that progressed during treatment with an AI for advanced/metastatic disease. Prior ovarian suppression and/or tamoxifen are allowed as long as the other criteria are met.~~

~~Subjects who have disease that has progressed during treatment with the combination of a CDK4/6 inhibitor (e.g., palbociclib) plus letrozole for advanced or metastatic disease. Prior ovarian suppression and/or tamoxifen are allowed as long as the other criteria are met.~~

~~Documented progression on the last line of systemic anti-cancer therapy is required.~~

~~During Phase I, up to 140 subjects may be enrolled. Two DLs will be studied; each DL will comprise two cohorts (each defined by most recent prior therapy) of up to 35 subjects each. The total number of subjects required will depend upon the totality of the data, including the safety and efficacy of each DL in each cohort.~~

Section 4.2.2: Treatment Arms and Duration

Rationale for change: The cohort DL 2 (80 mg) has been discontinued.

REVISED TEXT

Paragraph 1

Enrolment into DL2 has been discontinued. See Protocol Section 4.1.2 for the current design. ~~If both DLs are enrolling concurrently, subjects will be prioritized to the more recent dose level (e.g. DL2) until the sentinel group is filled. Subjects will then be enrolled into the first dose level (e.g. DL1) until the DL2 sentinel group has demonstrated that the second DL does not exceed the MTD. All additional subjects will then be randomized 1:1 to receive one of the two dose combinations.~~

Section 4.2.3.1: Planned Dose Levels

Rationale for change: DL 2 (80 mg) has been discontinued.

REVISED TEXT

Paragraph 1

The projected DLs of GSK525762 are 60 mg and 80 mg administered orally once daily. DL2 (80 mg) has been discontinued.

Section 4.2.3.2: Dose Level and Cohort Selection

Rationale for change: DL 2 (80mg) has been discontinued.

REVISED TEXT

Text deleted

~~Once this sentinel group of 3-10 evaluable subjects has cleared the DLT window at DL1, two cohorts will open at DL2. Subjects will be prioritized to treatment at DL2; any additional subjects enrolled prior to clearance of the DL2 sentinel group will be enrolled into one of the DL1 cohorts, based on their most recent prior treatment history. The DL2 DLT evaluation will occur as described for DL1, with a sentinel group of 3-10 evaluable subjects spread across the two cohorts.~~

~~If DL2 is found to be safe in this sentinel group, enrollment will be prioritized to DL2 until it enrols the same number of subject as DL1. After that, any eligible subject will be assigned 1:1 to either DL1 or DL2 until the cohort at either dose level is full or closed early for toxicity or lack of efficacy.~~

Paragraph 5

DL2 (80 mg) is discontinued.

Section 4.2.3.8: Intra-Subject Dose Escalation

Rationale for change: DL 2 (80 mg) has been discontinued

REVISED TEXT

Text added

After discontinuation of DL2 subjects will not automatically be reduced to DL1 if they have a favourable risk/benefit profile.

Section 4.2.5.1: Safety Analysis

Rationale for change: Updated subject numbers to reflect modified cohort analysis.

REVISED TEXT

The mTPI decision rule will be used for monitoring safety until ~~35~~30 subjects have been assigned at the same dose, at which time further enrollment will halt.

Section 4.2.5.2: Futility Analysis

Rationale for change: The cohort DL 2 (80 mg) has been discontinued

REVISED TEXT

For each cohort, the enrollment for that cohort may be stopped due to futility if the Bayesian ~~predictive~~ posterior probability that the confirmed response rate ≥25% in Cohort 1 (AI Failure) or ≥20% in Cohort 2 (CDK4/6+AI Failure) (target) is small (e.g., less than a 10% chance). For details, please see Section 9.4.

Section 4.3.2: Phase II Cohort Selection

Rationale for change: Letrozole has been expanded to include all AI agents.

REVISED TEXT

Paragraph 2, sub points 2 and 3

- CDK4/6 inhibitor plus ~~letrozole~~ AI, OR
- either AI therapy OR CDK4/6 inhibitor plus ~~letrozole~~ AI.

Section 4.4: Phase II Prior Treatment History Specific Cohorts

Rationale for change: Revised to reflect intent to redesign Part II.

REVISED TEXT:

Phase II will be redesigned based on the results for Phase I and the emerging data from literature ~~The treatment cohort and dose(s) taken into Phase II will be based upon the totality of data from Phase I~~.

Section 4.4.6: Data Review

Rationale for change: Minor update.

REVISED TEXT:

The schedule of any planned interim analysis and the analysis plan for IDMC review will be ~~is~~ described in the charter~~, which is available upon request~~.

Section 4.5.1: Phase I

Rationale for change: Revised criteria for modified Cohort 2.

REVISED TEXT:

The criteria will be based on a clinically ineffective response rate of 10% and 5% in Cohort 1 (AI Failure) and Cohort 2 (CDK4/6+AI Failure), respectively versus a clinically meaningful response rate 25% and 20% in Cohort 1 (AI Failure) and Cohort 2 (CDK4/6+AI Failure), respectively; the rationales for these response assumptions are described in Appendix 3.

Section 4.7.1: Risk Assessment

Rationale for change: Based on updates to the Molibresib Investigator's Brochure.

REVISED TEXT

For a full list of predicted and observed toxicities, refer to the GSK525762 Investigator's Brochure (IB) GlaxoSmithKline Document Number 2011N11374_07 and the FDA package insert for fulvestrant.

Section 4.7.1.1.1: Risk Assessment

Rationale for change: Based on updates to the Molibresib Investigator's Brochure.

REVISED TEXT

Paragraph 2

Gastrointestinal effects were frequently the dose-limiting toxicities in non-clinical animal studies of GSK525762. Dogs, ~~and~~ rats, and mice treated with repeated doses of GSK525762 experienced reduced body weight, ulceration/inflammation of the gastrointestinal (GI) tract, and abnormal feces. In study BET115521, drug-related ~~gastrointestinal~~ GI events were reported, as well. Drug related nausea was reported in 41%, decreased appetite was reported in 36%, diarrhea was reported in 32%, dysgeusia was reported in 30%, and vomiting was reported in 27% of subjects.~~Nausea was reported in 29% of subjects, dysgeusia was reported in 19%, decreased appetite was described in 17%, and diarrhea was reported in 16% of subjects~~. Gastrointestinal toxicity was predominantly Grades 1 and 2; 5~~3~~% of subjects reported Grade 3 nausea, 4% reported Grade 3 decreased appetite, 3% reported Grade 3 vomiting, and 2% of subjects reported Grade 3 diarrhea. ~~and 1% of subjects reported Grade 3 diarrhea~~. No Grade 4 ~~gastrointestinal~~ GI effects were observed. ~~Refer to the GSK525762 IB for full details.~~

Section 4.7.1.1.2: Hepatic Safety Findings

Rationale for change: Based on updates to the Molibresib Investigator's Brochure..

REVISED TEXT

Paragraph 2

GSK525762: In non-clinical animal studies, non-adverse liver changes were observed in rats, mice and dogs including increases in bilirubin levels in rats, increased bile acids in rats and mice and transient, reversible increased in AST and/or ALT in rats and dogs.

Hepatocellular necrosis was observed in a single rat at a non-tolerated dose. In the BET115521 clinical trial, liver effects have been noted. Cases of liver events meeting the definition of severe liver injury based on liver chemistries (ALT ≥3X ULN and Bilirubin ≥2X ULN) have been reported in study BET115521. Additional complicating factors were reported for these cases (e.g. liver metastasis and sepsis) with liver enzymes trending towards normal levels upon stopping GSK525762. Drug related elevated blood bilirubin was reported in 24%, aspartate aminotransferase (AST) elevation was reported in 11%, and alanine aminotransferase (ALT) elevation was reported in 8% of subjects. These drug related hepatic toxicities were predominantly Grades 1 and 2; 7% reported Grade 3 and <1% reported Grade 4 blood bilirubin increased and 2% of subjects reported Grade 3 AST increase. There were no Grade 4 ALT increases noted. ~~In non-clinical animal studies, non-adverse liver changes were observed in rats and dogs. Increased gall bladder vacuolation and; decreased cytoplasmic rarefaction in the liver was evident in dogs dosed at ≥1 mg/kg/day for 28 days. Necrosis was observed in one rat at 30 mg/kg/day in the 4 week study. In the BET115521 clinical trial, liver effects have been noted. Importantly, these effects appear isolated to the higher doses, and none have resulted in a pre-designated "liver event". At doses of 30 mg and below, no liver toxicity has been identified; one subject experienced Grade 3 hyperbilirubinemia but this was attributed by the investigator to the presence of extensive hepatic metastases and consequent liver dysfunction. Hyperbilirubinemia has been observed at 40 mg total daily dose and above in the solid tumor and hematologic malignancy studies. Approximately 21% of subjects treated with GSK525762 experienced elevated blood bilirubin; 4% of subjects (all in the solid tumor study) experienced Grade 3 hyperbilirubinemia. In addition, 8% of subjects experienced alanine aminotransferase (ALT) elevation (no Grade 3 or Grade 4 events were reported), and 6% of subjects experienced Aspartate aminotransferase (AST) elevation (one Grade 3 event was reported, in the solid tumor study). All liver findings resolved after the cessation of study drug. Refer to the GSK525762 IB for full details~~.

Section 4.7.1.1.3: Hematopoietic Safety Findings

Rationale for change: Based on updates to the Molibresib Investigator's Brochure.

REVISED TEXT

Paragraph 2, 3 and 4

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

In the BET115521 clinical trial, thrombocytopenia was observed, primarily at higher dose levels. ~~Forty-one percent (41%) of subjects reported thrombocytopenia of any grade, and 24% of subjects reported Grade 3-4 thrombocytopenia.~~ Thrombocytopenia was only noted after more than a week of continuous dosing, and platelet counts recovered after

cessation of the drug. Refer to the GSK525762 IB for full details. Drug related thrombocytopenia was reported in 59%, anemia was reported in 29%, international normalized ratio increased was reported in 14%, prothrombin time prolonged in 12% and coagulation factor VII level decreased in 10% of subjects. These AEs were mainly Grade 1 or 2; with Grade 3 thrombocytopenia reported in 22%, Grade 3 anemia reported in 12% and Grade 3 factor VII decrease in 4% of subjects. Grade 4 thromobocytopenia was reported in 16%, anaemia in 1% and factor VII decrease in 4% of subjects.

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

Section 4.7.1.1.5: General Toxicity Findings

Rationale for change: Based on updates to the Molibresib Investigator's Brochure..

REVISED TEXT

Section added

4.7.1.1.5: General Toxicity Findings

Fulvestrant: As described in the FDA package insert (Section 12.2), fulvestrant was associated with fatigue in 8% of subjects receiving the approved dose of 500 mg IM.

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

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

Section 4.7.1.2.1: Cardiovascular Safety Findings

Rationale for change: Based on updates to the Molibresib Investigator's Brochure.

REVISED TEXT

Paragraph 2 and 3

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

Monitoring and Management: Subjects will be monitored closely for changes in QTc with ~~triplicate~~ 12-lead ECG and for elevations in plasma troponin. Safety ECGs will be performed at the time points specified in Time and Events tables (Section 7.1) using a standard 12-lead ECG machine that automatically calculates the heart rate (HR) and

measures PR, QRS, QT and QTcF intervals. As clinically indicated, tThe mean from triplicate ECGs will be evaluated ~~at each time point~~.

Text deleted

~~In the BET115521 and BET116183 clinical trials, evaluation of cardiac safety data from subjects treated up to the 100 mg QD cohort by the cut-off date of May 15, 2015 demonstrated no significant QTc prolongation after single and repeat dose administration. Full analysis of cardiac safety data will be performed at the end of dose escalation in the BET115521 study. Refer to the GSK525762 IB for full details.~~

Section 5.1 Inclusion Criteria

Rationale for change: Updated to allow screening biopsy analysis and to develop predictive biomarkers of response to understand patient population that will significantly benefit from molibresib. The fulvestrant window of collection was added so that subjects do not need to repeat a biopsy as long as the most recent sample was after prior treatment. On therapy biopsy is not mandatory but is encouraged in order to evaluate for changes in molecular markers of molibresib inhibition and ER signaling. The pre and post dose biopsy samples was added to evaluate ER and ER target gene changes and/or other pathways altered by the combination treatment and provide a better understanding of molecular changes due to the combination treatment. The study does not need to be restricted to only letrozole because there are other treatments in this same class. Requirement of greater than or equal to 12 months of treatment is to evaluate subjects who had prolonged response to the prior treatments.

REVISED TEXT

Added Inclusion Criteria No. 6

6. Provision of mandatory screening fresh tumor biopsy sample during the screening period.
    a. Screening biopsy can be waived if a biopsy was collected within 3 months prior to first dose of study drug and was collected after the last anti-cancer treatment before coming into this study.
    b. Subjects with inaccessible site of biopsy or who have a significant medical risk of obtaining the biopsy should be discussed with the Medical Monitor if they can qualify.
    c. Bone biopsies are not acceptable. Biopsies should be obtained from bone with metastatic soft-tissue component. Subjects with bone only disease may be enrolled upon review by Medical Monitor.

Inclusion Criteria No. 7, 8 and 10

7. History of prior therapy that satisfies one of the following criteria:
    a. AI failures: Disease that relapsed during treatment or within 12 months of completion of adjuvant therapy with an AI, OR disease that progressed during treatment with an AI for advanced/metastatic disease. Prior

ovarian suppression and/or tamoxifen are allowed as long as other criteria are met.

b. CDK4/6 inhibitor plus ~~letrozole~~ AI failures: Disease that progressed on ~~during treatment with the combination of~~ a CDK4/6 inhibitor plus ~~letrozole~~ AI, for advanced/metastatic disease with a minimum duration of treatment of 12 months (≥12 mo) with CDK4/6 inhibitor plus AI. Subjects with either measurable disease or bone only disease are allowed. Prior ovarian suppression and/or tamoxifen are allowed as long as other criteria are met.

8. Documented progression on last line of systemic anti-cancer therapy with CDK4/6 inhibitor + AI is required.

10. Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria is required except for subjects with bone only disease.

Section 5.2 Exclusion Criteria

Rationale for change: Updates to the criteria for severe or uncontrolled systemic diseases were made to provide greater clarity. Update to criteria for baseline QTcF was based on review of QTc data from clinical studies with GSK525762 as described in the Molibresib Investigator's Brochure.

REVISED TEXT

Exclusion criteria no. 3, 8 and 11

3. ≥3 lines of systemic anti-cancer therapy in the advanced or metastatic setting.

NOTE:

a. Prior systemic anti-cancer therapy (cytotoxic chemotherapy, hormonal, CD4/6K inhibitor therapies) in the neoadjuvant/adjuvant setting does not count toward the lines of therapy.

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

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

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

11. Cardiac abnormalities as evidenced by any of the following:

- Baseline QTcF interval ≥4~~5~~50 msec

Section 5.4 Withdrawal/Stopping Criteria

Rationale for change: To include requirement that the Medical Monitor (MM) should be consulted before a subject can discontinue one agent and continue on the other.

REVISED TEXT

Paragraph 12

Subjects who require permanent discontinuation of one of the study treatments in a given combination may continue on the other treatment until disease progression, withdrawal of consent, or unacceptable toxicity after discussion with Medical Monitor.

Section 5.4.2. QTc Stopping Criteria

Rationale for change: To update to QTc stopping criteria.

REVISED TEXT

Paragraph 2
Study treatments will be withheld if either of the following occurs:

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

Section 6.2.2 Phase II

Rationale for change: Letrozole has been expanded to include all AI agents.

REVISED TEXT

Subjects who have disease that has progressed after prior treatment with either AIs or CDK4/6 inhibitor plus ~~letrozole~~ AI will be randomized 1:1 to receive either fulvestrant plus GSK525762 or fulvestrant plus GSK525762-matched placebo. Subjects will be assigned to their cohort in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

Section 6.3. Planned Dose Adjustments

Rationale for change: Removal of former Section for consistency with other modifications in the protocol and IB.

REVISED TEXT

Section 6.3.1 deleted

~~**6.3.1 Guidelines for Events of Special Interest**~~

~~Events of special interest are defined in Appendix 10. The severity of adverse events (AEs) will be graded utilizing the National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment(s) are provided in Appendix 2.~~

Section 6.4. Blinding

Rationale for change: Letrozole has been expanded to include all AI agents.

REVISED TEXT

Paragraph 2

Phase II of the study will double-blind. Based on results from Phase I, Phase II will enroll subjects who have disease that has progressed after prior therapy with:

- AIs alone (either in the setting of primary metastatic disease or on-treatment/within 12 months of discontinuing adjuvant endocrine therapy), OR
- CDK4/6 inhibitor plus ~~letrozole~~AI, OR
- either AI therapy OR CDK4/6 inhibitor plus ~~letrozole~~AI. If both cohorts are permitted to enroll in Phase II, randomization will be stratified by prior CDK4/6 inhibitor-based therapy (i.e., CDK4/6 inhibitor-naïve versus CDK4/6 inhibitor-exposed) and corresponding stratified analysis will be provided at interim and final analyses

Section 6.11.1 Permitted Medications and Non-Drug Therapies

Rationale for change: To include granulocyte colony-stimulating factors (GCSF) as permitted medication since GCSF is frequently used as supportive care in patients with breast cancer and should be included as an option for subjects when clinically indicated.

REVISED TEXT

Paragraph 1

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, granulocyte colony-stimulating factors (GCSF) and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate. The only caveat is that subjects should not receive those medications listed as prohibited in Section 6.11.2.

Section 6.11.2.1 Prohibited Medications

Rationale for change: Update to wording, removal of former Table 4 based on review of cardiac safety data from clinical studies with GSK525762 as reflected in the Molibresib Investigator's Brochure.

REVISED TEXT

Paragraph 2

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

Text deleted

~~Co-administration of the medications listed in Table 4 are prohibited for 5 half-lives (or at least 14 days, whichever is longer) prior to the first dose of study drug until discontinuation from the study drug due to unacceptable risk of Torsades de Pointes (with the exception of amiodarone, which is prohibited beginning 6 months prior to screening through discontinuation from the study. [However, there may be situations when the subject is on study and Advanced Cardiac Life Support (ACLS) requires the use of amiodarone, which should be used as per local clinical guidelines]).~~

~~These medications include (but are not limited to):~~

~~Table 4 Drugs with a Risk of Torsades de Pointes that are Prohibited~~

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

~~Data Source: crediblemeds.org revision date 09 Jan 2017. The above table is not exhaustive. Please refer to a database like crediblemeds.org for updates at the time of screening a subject, since these are dynamic lists that change based on new information which cannot be updated on a static table.~~

Section 6.11.2.2 Prohibited Non-Drug Therapies

Rationale for change: Update to include cclarification regarding both prescription and non-prescription herbal preparations/medications. Herbal medication language further clarified to avoid unknown interactions.

REVISED TEXT

Paragraph 2

Subjects will abstain from using herbal prescription/non prescription preparations/medications throughout the study until the final study visit due to the limited data on potential CYP-mediated interactions produced by those products. Herbal products include, but are not limited to: St. John's Wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, ginseng, and marijuana.

Section 6.11.2.3 Cautionary Medications

Rationale for change: Update to wording, removal of former Table 5 based on review of cardiac safety data from clinical studies with GSK525762 as reflected in the Molibresib Investigator's Brochure.

REVISED TEXT

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

If a subject requires medication for hyperemesis, due to the potential of serotonin 5-HT3 receptor antagonists to increase QT duration corrected for heart rate by Fridericia's formula (QTcF), palonosetron (administered per the prescribing information) and ondansetron (up to a maximum dose of 8 mg three times daily [TID]) are the only allowed drugs in this class. Intravenous administration is not allowed. Drugs with a low risk of causing QTc prolongation (e.g., aprepitant) may be used without restriction.

Co-administration of GSK525762 and medicines which may have an increased risk of Torsades de Pointes ~~the following medications~~ requires extreme caution beginning 14 days prior to the first dose of study drug until discontinuation from the study~~, due to an increased risk of Torsades de Pointes~~. Please reference the current list of medications at ~~www.crediblemeds.org~~ ~~These medications include (but are not limited to):~~

Table 5 Drugs with a Risk of Torsades de Pointes which are permitted for co-administration with Extreme Caution

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

Data Source: crediblemeds.org revision date 09 Jan 2017. The above table is not exhaustive. Please refer to a database like crediblemeds.org for updates at the time of screening a subject, since these are dynamic lists that change based on new information which cannot be updated on a static table.

Section 7.1. Time and Events Table

Rationale for change: Updates regarding ECGs, requirement of fresh biopsies at screening and collection window, clarification of requirements around fresh tumor biopsies sample and other general clarifications.

REVISED TEXT

Table 5: Time and Events, Phase I

Procedure	SCR	Week 1		Week 2		Week 3		Week 4	Week 5	q4w	q8w	q8w	q12w	EOT[1]
		D1	D4	D1	D4	D1	D4	D1	D1	W9 to W49	W9 to W49	W49 and thereafter	W49 and thereafter	
Safety														
12-lead ECGs ~~(Triplicate)~~[6]	X	X	X	X		X		X	X	X			X	X
Pregnancy test[5]	X	X				X			X		X		X	X
Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)														
Tumor biopsy[12]	X						One sample, collected between W3D4 and W5D4~~1~~, as close as possible to 3-6h post-GSK525762 dose							X[13]

6. Triplicate ECGs should be performed at screening. All other timepoints can be single ECGs prior to dosing and evaluated for abnormality prior to administration of dose. Post Week 49, assessments will be completed every 12 weeks. Triplicate ECGs to be performed as clinically indicated, based upon abnormal findings.

8. Whatever scanning modality is used at screening should be maintained for all subsequent scans. An assessment is not performed at W9. Beginning at W13, scans will be performed once every 12 weeks.

12. Mandatory Screening ~~(archival)~~ tumor biopsy specimen is required for all subjects; ~~if archival sample is not available then fresh specimen must be provided~~ within 28~~14~~ days prior to first study dose as described in Section 7.5.1. ~~Paired fresh biopsies must be provided pre- and on-treatment at the time points indicated for at least 6 subjects (out of 35 planned for enrollment) at each dose level~~. Subjects providing an optional on-treatment fresh tumor biopsy, whether they have had a dose interruption of GSK525762 or not, must have received at least 4 consecutive doses of GSK525762 prior to the collection of the tissue. If the post-dose biopsy is not performed during this timeframe due to lab abnormalities or subject status, it should be performed at the next agreed upon visit with the medical monitor after subject recovery. ~~A limited number of additional subjects may be requested to provide pre- and on-treatment biopsies based on emerging data.~~ Fresh biopsies should be paired with plasma samples for PK, collected as close as possible to biopsy (ideally within 1 h). Subjects must have a platelet count of ≥75,000/mm^3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy, or any other planned surgical procedure. Refer to the SRM for further details.

Table 6: Time and Events, Phase I Laboratory Assessments

	SCR [1]	Week 1		Week 2		Week 3		Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 11	q4w	q12w	EOT
		D 1	D 4	D 1	D 4	D1	D4	D1	D1	D1	D1	D1	D1	D1	W13 and after	W49 and after	
Pregnancy test[5]	X	X				X			X		X		X	X	X	~~X~~	X

Table 7: Time and Events, Phase II

Procedure	SCR	Week 1		Week 2	Week 3	Week 4	Week 5	q4w	q8w	q8w	q12w	EOT[1]
		D1	D4	D1	D1	D1	D1	W9 to W49	W9 to W49	W49 and thereafter	W49 and thereafter	
Safety												
12-lead ECGs ~~(Triplicate)~~[6]	X	X	X	X	X	X	X	X			X	X
Pharmacokinetics (PK), Translational Studies & Pharmacogenomics (PGx)												
Tumor biopsy ~~(archival)~~[12]	X											X[13]

6. Triplicate ECGs should be performed at screening. All other timepoints can be single ECGs prior to dosing and evaluated for abnormality prior to administration of dose. Post Week 49, assessments will be completed every 12 weeks. Triplicate ECGs to be performed as clinically indicated, based upon abnormal findings.

8. Whatever scanning modality is used at screening should be maintained for all subsequent scans. An assessment is not performed at W9. Beginning at W13, scans will be performed once every 12 weeks.

Patient Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Item Library (Version 1.0). Post Week 49, assessments will be completed every 8 weeks.

12. Screening ~~(archival)~~ tumor biopsy specimen is required for all subjects; ~~if archival sample is not available then~~the fresh specimen must be provided within ~~14~~ 28 days prior to first study dose. It is acceptable to collect tumor biopsy specimen within the screening period. A sample collected within 3 months of first dose is also acceptable only if it was collected after the last anticancer treatment. Refer to Section 7.2.1 and to the SRM for further details. Subjects must have a platelet count of ≥75,000/mm3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy, or any other planned surgical procedure.

Table 8: Time and Events, Phase 2 Laboratory Assessments

	SCR [1]	Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 11	q4w	q12w	EOT
		D1	D 4	D1	D1	D1	D1	D1	D1	D1	D1	D1	W13 and after	W49 and after	
Pregnancy test[5]	X	X			X		X		X		X	X	X	~~X~~	X

Section 7.2.1. Critical Baseline Assessments

Rationale for change: Biopsy collection was updated to fulfil exploratory pharmacodynamic analysis of tumor tissue. Flexibility was included to allow subjects who are not able to undergo a biopsy a means of still enrolling in the trial. On treatment biopsy is clarified as optional and requirement of 6 paired samples is removed to avoid excluding subjects who are not able to undergo a biopsy.

REVISED TEXT

A baseline tumor biopsy sample is required for all subjects, as follows:

- Phase I:
  - All subjects must provide a biopsy sample at screening. ~~Archival tissue is permitted; however, if no archival tissue is available then a~~ A fresh biopsy specimen must be provided within 28~~14~~ days prior to first study dose. A sample collected within 3 months of first dose is also acceptable only if it was collected after the last anticancer treatment.
  - Subjects with bone only disease without any visceral tumor tissue amenable to biopsy may be enrolled without a biopsy sample only upon review by medical monitor
  - Paired on treatment fresh biopsies are optional but encouraged. All~~t east 6~~ subjects enrolled in the study ~~at each dose level~~ will be asked~~required~~ to provide paired fresh biopsies pre- and post-dose at the time points indicated in Section 7.1, as described in Section 7.5.1. Fresh biopsies should be paired with plasma samples for PK, collected as close as possible to the biopsy (ideally within 1 h). Subjects should have at least four consecutive doses of GSK525762 prior to collection of tumor biopsy, whether they have had a dose interruption or not. Subjects will be informed at the time of informed consent whether paired fresh biopsies will be required. If a potential subject does not have a disease amenable to biopsy, participation may occur only upon discussion and approval of the medical monitor Further details regarding sample type and processing will be provided in the SRM.
- Phase II:
  - All subjects must provide ~~an archival~~a fresh tissue specimen at screening. If an archival specimen is not available, then a fresh pre-treatment biopsy specimen must be provided. On-study biopsies are not required

Section 7.2.2. Visit Windows

Rationale for change: Clarification regarding PK sample collection for subjects with interrupted dosing.

REVISED TEXT

Paragraph 5 and 8

Week 3: Assessments on Week 3 Day 1 may be delayed up to 2 days. Assessments on Week 3 Day 4 may be scheduled ± 3 days.

Note: The Week 3 Day 1 PK collection is timed to permit evaluation of GSK525762 PK at steady-state dosing (at least 7 consecutive days dosing prior to collection). If a subject is not receiving GSK525762 on Week 3 Day 1 (~~either as a consequence of a planned drug holiday or~~ due to toxicity), then serial PK collection should be rescheduled for a later timepoint when the subject is again being dosed for at least 7 consecutive days~~at steady state~~, and the alternate collection date noted in the eCRF. However, in this case a single pre-dose sample should still be collected to evaluate for fulvestrant trough concentration.

Every 4-week and 8-week visits after Week 9 until Week 49: After the first disease assessment has been completed, then the clinic visits can be scheduled ± 5 days. During visits with planned PK sample collection, for subjects who have interrupted dosing, the collection should be postponed until the subject has received at least 7 consecutive doses of GSK525762.

Section 7.3.3.1 Electrocardiograms

Rationale for change: Update to guidelines for electrocardiograms assessments.

REVISED TEXT

Paragraph 1 and 2

Triplicate 12-lead ECGs will be obtained at screening. On treatment single ECGs will be completed, prior to dosing, on days specified in Section 7.1 during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Details will be provided in the SRM. Any values >48~~5~~0 msec as calculated by the machine must be confirmed manually according to Fridericia's formula. Refer to Section 5.4.2 for QTcF calculations and QTc withdrawal criteria, and to Appendix 2 for management strategies for QTcF prolongation. Triplicate ECGs should be performed as clinically indicated, due to abnormal findings.

~~Baseline results are defined by the nearest timepoint prior to first dose. For this trial~~ T~~t~~he baseline QTcF value is determined by the mean of the triplicate ~~W1D1 predose QTcF results. If these results are not available, then the mean QTcF of the~~ screening ~~triplicate~~ ECG results ~~should be used~~.

Section 7.3.4. Clinical Safety Laboratory Assessments

Rationale for change: Update to Table for Clinical Laboratory tests regarding collection of troponin and adding a list of acronyms in the footnotes.

REVISED TEXT

Table 9 Clinical Laboratory Tests

Cardiac Studies		
Troponin (I or T), may be collected at central laboratory if local draw is not possible NT-proBNP Fasting Lipid panel (Total Cholesterol, LDL, HDL, triglycerides)		
Other Studies		
Coagulation Studies:	**Endocrine Studies:**	**Safety Screening Studies:**
Prothrombin Time/INR	Thyroid-stimulating hormone (TSH)	
Partial Thromboplastin Time or Activated Partial Thromboplastin Time (aPTT)	Free Thyroxine 3 (Free T3)	HIV, HbSag, HCV antibody
Fibrinogen	Free Thyroxine 4 (Free T4)	**Pancreatic Markers:**
Factor VII Assay	Hemoglobin A1c	Amylase
	FSH and estradiol (for pre- and peri-menopausal subjects only)	Lipase

*Direct and/or calculated BUN values are acceptable.

**Direct Bilirubin is only required if total bilirubin values are abnormal.

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

Section 7.5 Pharmacodynamics

Rationale for change: Biopsy collection was updated to fulfil exploratory pharmacodynamic analysis of tumor tissue.

REVISED TEXT

Tumor samples will be collected pre-dose and on-treatment from a limited number of subjects in order to evaluate for changes in molecular markers of BET inhibition (e.g., expression of proteins regulated by BET proteins) and ~~ER~~HR signal~~l~~ing.

Section 7.5.1 Tumor Biopsy Collection/Surgical Procedures

Rationale for change: Update to guidance regarding screening and on treatment biopsies as noted above.

REVISED TEXT

A mandatory fresh tumor biopsy sample is required for all subjects during the screening period within 28 days of the first dose of study treatment. A sample collected within 3 months of first dose is also acceptable only if it was collected after the last anti-cancer treatment. Bone biopsy sample is not acceptable. Biopsy requirement for subjects with bone only disease with no visceral tumor may be waived only upon review by GSK.

a. Screening biopsy can be waived if a biopsy was collected within 3 months prior to first dose of study drug and was collected after the last anti-cancer treatment before coming into this study.
b. Subjects with inaccessible site of biopsy or who have a significant medical risk of obtaining the biopsy should be discussed with the Medical Monitor if they can qualify.

c. Bone biopsies are not acceptable. Biopsies should be obtained from bone with metastatic soft-tissue component. Subjects with bone only disease may be enrolled upon review by Medical Monitor.

~~In Phase I, paired fresh biopsies must be provided pre- (within 14 days prior to the first dose) and on-treatment at the time points indicated for at least 6 subjects (out of 35 planned for enrollment) at each dose level.~~ On treatment fresh biopsies are optional but encouraged. Subjects providing an on-treatment fresh tumor biopsy must have received at least 4 consecutive doses of GSK525762 prior to the collection of the tissue. A limited number of additional subjects may be requested to provide pre and on-treatment biopsies based on emerging data. Biopsy requirement(s) will be discussed with the subject prior to signing informed consent. Any fresh on-treatment biopsy should be accompanied by a plasma sample collected as close as possible to the time of biopsy (preferably within 1 h).

Section 7.7.1 Tumor Biomarker Analysis

Rationale for change: As noted above**.**

REVISED TEXT

To further characterize the subject population, DNA, RNA and/or protein measurements may be utilized to identify predictors of sensitivity or resistance to GSK525762 and fulvestrant in combination utilizing baseline tissue (archival tissue or a recent biopsy) and tissue obtained at disease progression (if sample is available). Further details on sample requirements and collection will be provided in the SRM.

Section 7.7.2 Tumor Tissue

Rationale for change: Update to guidance regarding screening and on treatment biopsies

REVISED TEXT

All enrolled subjects in the study will be ~~asked~~ required to submit a~~n archival~~ fresh tumor biopsy at screening ~~baseline~~ in order to conduct retrospective tests for the identification and/or validation of known and novel biomarkers. ~~If an archival specimen is not available,~~ A~~a fresh biopsy will be required~~. Further details on sample requirements and collection will be provided in the SRM.

~~A small number of subjects (at least 6 per dose level) enrolled in Phase I must submit fresh tumor biopsies collected pre- and post-dose as described in Section 7.5.1 and the SRM.~~

Optional on-treatment tumor biopsy S~~s~~amples will be analyzed using appropriate technologies including, but not limited to, RNAseq, exome or targeted DNA sequencing, IHC, and/or qRT-PCR.

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

Section 9.1.2 Phase I Efficacy

Rationale for change: The statistical analysis plan was updated to provide details of analysis for Cohort 2.

REVISED TEXT

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 objective response rate (CR + PR) of 25% relative to a 10% response rate suggesting no activity. This will be conducted by testing the null hypothesis that P0<=0.1 versus the alternative that P1 >0.25, 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 the measurable disease subjects only, defined as an objective response rate (CR + PR) of 20% relative to a 5% response rate suggesting no activity. This will be conducted by testing the null hypothesis that P0<=0.05 versus the alternative that 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 (AI Failure) and (0.005, 0.095) for Cohort 2 (CDK4/6+AI Failure) is used, which is equivalent to the information present in 0.1 subjects. ~~A secondary endpoint for Phase I is to demonstrate a clinically meaningful response ratio (RR), defined as an ORR (confirmed CR + confirmed PR) of 25% relative to a 10% ORR suggesting no activity. This will be conducted by testing the null hypothesis that P0<=0.1 versus the alternative that P1 >= 0.25, assuming the maximum RR for an ineffective drug is 10% and the minimum RR for an effective drug is 25%. This portion of the study will employ the Bayesian method that allows the trial to be frequently monitored with the constraint of controlling both Type I and Type II error rates. Enrollment to an individual cohorts may be stopped early for toxicity or lack of efficacy, but will not be stopped early if the ORR meets or exceeds the alternate hypothesis at the interim analyses. The rationale for selecting these response rates is detailed in Appendix 3.~~

~~The Phase I portion of the study will employ a Bayesian predictive adaptive design [Lee, 2008] that allows the trial to be monitored more frequently at multiple stages. The criteria will be based on a historically unimportant ORR of 10% versus an ORR of interest of 25%. Bayesian statistics will be employed to calculate the predictive probability that the RR ≥25% and ≥10% at interim assuming a Beta prior for the Binomial distributed data. Predictive probability calculates the probability that the RR ≥25% or ≥10% given the responses have already been observed. A weak prior Beta (0.0125, 0.0875) is used, which is equivalent to the information present in 0.1 subjects. The first interim analysis may be conducted when at least 10 evaluable subjects are available for each cohort at a given dose. Futility interim analysis decision rules for the 10th to 34th evaluable subjects, specifying the number of subjects with a confirmed response needed for continuing enrollment or stopping for futility when total sample size is up to 35 in a particular cohort is presented in Table 10. These rules are intended as a guideline. Actual decisions will depend on the totality of the data.~~

Table 10 Decision Making Criteria for Futility

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

For the separate interim looks in each cohort, the enrollment for that cohort may be stopped due to futility if the predictive probability that the confirmed RR ≥25% is small (e.g., less than a 4% chance for a total sample size of 35 subjects). Enrollment 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 less than 1 confirmed responses are observed in the first 14 evaluable subjects. The evaluable subject is defined as a subject, who has either progressed or died, withdrew from the study treatment, or is ongoing and has completed at least two post treatment disease assessments. For example, when there are 14 evaluable subjects available at the time of interim analysis with only one response, then the cohort may be stop for futility. Otherwise, the enrollment of the respective cohort will continue to the target sample size.

~~When the total sample size in a treatment arm is 35 and at least 6 responders out of 35 subjects are observed, we can claim null hypothesis is rejected and the phase 2 part on that cohort and dose may follow.~~

~~The ORR and safety endpoints will be jointly assessed using a utility function when both DL1 and DL2 are safe and effective. The dose with the best utility function may be picked as RP2D for Phase 2. The details of the utility function calculations will be discussed in Reporting and Analysis Plan (RAP). This calculation is for guidance only, the final decision of RP2D will be based on totally of data.~~

Section 9.2.1.1 Phase I

Rationale for change: The requirement of subjects with ≥ 12 months of prior treatment was added to evaluate subjects who have experienced prolonged response. Subjects with bone only disease were added to reflect 30% of the metastatic breast cancer population.

REVISED TEXT

Up to ~~70~~ 35 measurable disease subjects per DL in Cohort 1 and 32 measurable disease subjects per DL in Cohort 2 ~~will~~ may be enrolled ~~into two cohorts (based on prior therapy) at each DL (approximately 35 per cohort)~~ to collect safety/tolerability, PK, PD, and efficacy data. Sixteen additional bone only disease subjects will be enrolled into DL1 cohort 2. Additional subjects may be enrolled at, or below the combination doses, in order to collect additional safety and PK data.

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

In Cohort 1 (AI Failure) the null and alternative hypotheses are:

H_0: ORR≤10%

H_A: ORR≥25%

When maximum sample size is 35, the design will have a Type I error (α) of 0.098 and 80% power.

In Cohort 2 (CDK4/6+AI Failure) the null and alternative hypotheses are:

H_0: ORR≤5%

H_A: ORR≥20%

When maximum sample size is 32, the design will have a Type I error (α) of 0.0535 and 81% power.

Section 9.3.2.1.2 Efficacy Analyses

Rationale for change: The statistical plan was updated to reflect modification of Cohort 2.

REVISED TEXT

Interim analyses during expansion cohorts

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. Enrollment may be stopped early in any of the expansion cohorts for toxicity or lack of efficacy, should various criteria occur based on accrued data. The decision criteria for early stop for futility based on Bayesian Hierarchical model are described below. The decision will be made for each individual prior treatment history-specific cohort.

For the separate interim looks in each cohort, the enrollment 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). Enrollment 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 less than 2 confirmed responses are observed in the first 14 and 19 evaluable subjects in Cohort 1 and Cohort 2, respectively. The evaluable subject is defined as a subject, who has either progressed or died, withdrew from the study treatment, or is ongoing and has completed at least two post treatment disease assessments. For example, when there are 14 evaluable subjects available at the time of interim analysis with only one response, then the cohort may be stop for futility. Otherwise, the enrollment of the respective cohort will continue to the target sample size.

Futility interim analysis decision rules for the 10^{th} to 34^{th} evaluable subjects in Cohort 1 (AI Failure) and 10^{th} to 32^{nd} evaluable subjects in Cohort 2 (CDK4/6+AI Failure), specifying the number of subjects with a confirmed response needed for continuing enrollment or stopping for futility when total sample size is up to 35 in Cohort 1 (AI Failure) and up to 32 in Cohort 2 (CDK4/6+AI Failure) is presented in Table 10and 11, respectively. These rules are intended as a guideline. Actual decisions will depend on the totality of the data.

Table 10 Decision Making Criteria for 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 11 Decision Making Criteria for 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

Additionally, the ORR and safety endpoints will be jointly assessed using a utility function when both DL1 and DL2 are safe and effective. The dose with the best utility function may be picked as RP2D for Phase 2. The details of the utility function calculations will be discussed in Reporting and Analysis Plan (RAP). This calculation is for guidance only, the final decision of RP2D will be based on totally of data.

The study population used for decision-making at the interim analyses on efficacy will be termed All Evaluable Subjects. ~~This will be the population for Bayesian model and summaries of response if data warrant. Because subjects enroll at different times, not all subjects will have been on the study long enough to have single or multiple disease assessments.~~ Since disease assessments are to be completed every 8 weeks, subjects who have at least two post-baseline radiological disease assessments or have progressed or died or permanently withdraw from the study treatment will be included in this population. Interim analysis on safety will be conducted on all treated subjects.

Section 9.4.8.1 Phase I

Rationale for change: The statistical plan was updated to reflect modification of Cohort 2.

REVISED TEXT

Paragraph 1

For the Phase I final analysis, each dose and cohort will be analyzed separately. In Cohort 2 (CDK4/6+AI Failure), measurable disease subjects and bone only disease subjects will be analyzed separately and combined within a dose. However, bone only disease subjects will not be evaluated for ORR. The focus of analyses that contain bone only disease subjects will be DCR, PFS and OS.

Paragraph 3

The observed confirmed and unconfirmed ORR will be reported at the interim and final analysis for each cohort specified in Phase 1 treated dose, if data warrant. The estimates along with 95% exact confidence interval (CI) will be provided. Bayesian inference based on summary statistics from the posterior distributions of each ORR will be reported at interim and final analyses. The posterior mean and posterior 2.5% and 97.5% percentiles of the ORR will be calculated for each cohort. In addition, the ~~predictive~~ posterior probability that the ORR exceeds its corresponding historical control will be reported for each cohort.

Section 11: References

Rationale for change: Information from updated IB was used

REVISED TEXT

~~GlaxoSmithKline Document Number 2011N113741_05. Investigator Brochure for GSK525762. Report Date 28-Mar-2016~~

GlaxoSmithKline Document Number 2011N113741_07. Investigator Brochure for GSK525762. Report Date 18-May-2018

Section 12.1 Appendix 1: Abbreviations and Trademarks

Rationale for change: Addition of abbreviation.

REVISED TEXT

Table of Abbreviation

GCSF	Granulocyte Colony-Stimulating Factors
HR+HER2-	Hormone Receptor-positive, HER2-negative

Section 12.2 Appendix 2: Management of Suspected Toxicity

Rationale for change: Update to toxicity management for QTcF events in Appendix 2 and explanation for reconsent.

REVISED TEXT

Table 12: Dose Adjustment/Stopping Safety Criteria

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

	If ≥ 60 msec change from baseline occurs ~~OR~~AND QTcF ≥500 msec ~~AND~~OR QTcF ≥530 msec And <60 msec change from baseline (average of three ECGs over at least 15 minutes)	Discontinue GSK525762 and notify the Medical Monitor. • Evaluation by cardiologist • Supplement electrolytes to recommended levels: e. Maintain serum potassium > 4mol/L f. Maintain serum magnesium levels >0.85 mmol/L • Rule out other potential etiologies for prolonged QTcF such as cardiac ischemia • Discontinue any concomitant medications with potential for QTcF prolongation. • 24-hour telemetry monitoring if clinically indicated. This subject may consider ~~re~~starting study treatment at a one dose level reduced if all of the following criteria for QTcF re-challenge are met. If approval for re-challenge is granted, the subject must be re-consented (with a separate informed consent specific to QTc prolongation) (7) QTcF reduced to <485~~0~~ msec, (8) Potassium and magnesium levels are within institutional normal range, (9) A favorable risk/benefit profile (in the medical judgement of the Investigator and the Medical Monitor), (10) Approval within GSK medical governance: a. agreement with SERM MD and PPL, b. review with Chair or co-Chair of the GSK QT panel, c. SERM VP and Clinical VP approval d. Head Unit Physician approval (11) The subject is re-consented regarding the possible increased risk of QTc prolongation. • Discontinuation procedures: If the subject is withdrawn due to QTcF event, the subject should complete the following activities post-dose: (4) Evaluation by cardiologist. (5) Weekly assessments for QTcF until ≤30 msec change from baseline reached, and then next assessment at 4 weeks post-dose. (6) If QTcF results have not resolved to baseline by 4 weeks post-dose, then continue every 4-5 weeks until resolution

Footnote added:

c. Fulvestrant should be restarted following the original schedule.

Section 12.3.2 Phase 2

Rationale for change: Minor update to include all AI inhibitors consistent with Part 1.

REVISED TEXT

The statistical design in Phase 2 of this study is based upon the hypothesis that the combination of fulvestrant plus GSK525762 will double the PFS (i.e., a hazard ratio of 0.5) compared to fulvestrant alone (for subjects previously treated with AI and/or CDK4/6 inhibitor/~~letrozole~~AI) or compared to SoC (for subjects previously treated with CDK4/6 inhibitor/fulvestrant). This value is comparable to the PFS improvement identified in the palbociclib/fulvestrant study (HR=0.46; [Cristofanilli, 2016] as well as the everolimus/exemestane study (HR=0.43; [Baselga, 2012]).

Section 12.4 Appendix 4: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

Rationale for change: Updated to clarify that elective termination for non-medical reasons do not require additional collection of data.

REVISED TEXT

Section number added

12.4.1. Contraception Guidance:

Section 12.4.2 Collection of Pregnancy Information

Rationale for change: Collection of pregnancy information regarding elective termination is clarified that only those performed due to medical reasons are required to be reported

REVISED TEXT

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

12.14.6. Amendment 06

Protocol changes for Amendment 06 (06-MAY-2020), from protocol changes to amendment 05 (11-SEP-2018)

Protocol Amendment 06 applies to all global site(s) participating in the conduct of the study

Amendment 06 summary:

Amendment 06 applies to all global study sites. These changes are based on decision to close out the study and stop all new enrolment based on interim data failing to demonstrate meaningful clinical benefit in the proposed patient population.

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. Enrolment into the study is now closed. The study will conclude when the last subject has completed/discontinued study treatment and completed the end of treatment visit.

Changes to the protocol include:

- Enrolment into the study is now closed.
- Removes the requirement for specific protocol assessments and survival follow-up (Section 7.1 – Time and Events Tables)
- Updates to contraceptive measures required for study participants, based upon January 2020 updates to the fulvestrant Summary of Product Characteristics
- Update to the GSK signatory and GSK medical monitor
- Provides updated guidance for subjects who have discontinued combination treatment and are on fulvestrant monotherapy
- Provides clarification on clinical supply dosages available for the study
- Administrative changes including minor clarifications, formatting and typographical errors

List of Specific Changes

Text which has been added to the protocol is indicated in Appendix 12 by underlined text. Text which has been deleted from the protocol is indicated in Appendix 12 by ~~strike through~~ format.

Title Page

Rationale for change: Update to protocol author list

REVISED TEXT

Author (s): PPD [redacted]

Section Title Page-Sponsor Signatory

Rationale for change: Update to sponsor signatory

REVISED TEXT

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Section Title Page-MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Rationale for change: Update to Medical Monitor information

REVISED TEXT

Medical Monitor/SAE Contact Information:

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

Section 1: protocol synopsis

Rationale for change: These changes are based on the decision to close out the study and stop all new enrolment based on interim data failing to demonstrate meaningful clinical benefit in the proposed patient population.

REVISED TEXT

Objective(s)/Endpoint(s)

Phase I

With the implementation of amendment 06, Phase I of the study is closed to enrolment.

Phase II

With the implementation of amendment 06, Phase II of the study is terminated.

Study Schematic

Phase I:

With the implementation of amendment 06, Phase I of the study is closed to enrolment.

Phase II:

With the implementation of amendment 06, Phase II of the study is terminated.

Number Of Subjects

Analysis

Third and fourth paragraph

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. Enrolment into the study is now closed as interim data failed to demonstrate meaningful clinical benefit in this patient population.

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. There will be no Phase II.

Section 3 OBJECTIVE(S) AND ENDPOINT(S)

Rationale for change: These changes are based on the decision to close out the study and stop all new enrolment based on interim data failing to demonstrate meaningful clinical benefit in the proposed patient population.

REVISED TEXT

Phase I

With the implementation of amendment 06, Phase I of the study is closed to enrolment.

Phase II

With the implementation of amendment 06, Phase II of the study is terminated.

Section 4.1.1. Original Overall Design (Protocols 01-04)

Rationale for change: These changes are based on the decision to close out the study and stop all new enrolment based on interim data failing to demonstrate meaningful clinical benefit in the proposed patient population. Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

REVISED TEXT

Phase I tenth paragraph onwards

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. Enrolment into the study is now closed as interim data failed to demonstrate meaningful clinical benefit in this patient population.

With the implementation of Amendment 06, specific assessments and collection of survival follow-up data will no longer be required. Please see Section 7.1 for further

details. The study will conclude when the last subject has completed/discontinued study treatment and completed the end of treatment visit. There will be no Phase II.

Section 4.3. Decision to Proceed to Phase II

Rationale for change: These changes are based on the decision to close out the study and stop all new enrolment based on interim data failing to demonstrate meaningful clinical benefit in the proposed patient population.

REVISED TEXT

With the implementation of amendment 06, Phase II of the study is terminated.

Section 4.5.1. Phase I

Rationale for change: These changes are based on the decision to close out the study and stop all new enrolment based on interim data failing to demonstrate meaningful clinical benefit in the proposed patient population. Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

REVISED TEXT

Fourth paragraph onwards

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. Enrolment into the study is now closed.

With the implementation of Amendment 06, specific assessments and collection of survival follow-up data will no longer be required. Please see Section 7.1 for further details. The study will conclude when the last subject has completed/discontinued study treatment and completed the end of treatment visit.

Section 4.7.1.1.4. Reproductive Safety Findings

Rationale for change: Updates to contraceptive measures required for study participants, based upon January 2020 updates to the fulvestrant Summary of Product Characteristics have been added to Appendix 4.

REVISED TEXT

Monitoring and Management: Based on the findings in these reproductive and developmental toxicity studies in animals with both fulvestrant and GSK525762, there is a substantiated risk for adverse effects on embryo-fetal development and impacts on female fertility. Consequently, the proposed study will include strict contraceptive requirements for females of child-bearing potential (Section 6.10.2), described in Appendix 4. Pregnancy tests will be required at screening and periodically during the study for all women of child-bearing potential, as indicated in the Time and Events table

(Section 7.1). Women who become pregnant while on study will be required to discontinue therapy and will be followed as described in Appendix 4.

Section 5.1. Inclusion Criteria

Rationale for change: Updates to contraceptive measures required for study participants, based upon January 2020 updates to the fulvestrant Summary of Product Characteristics have been added to Appendix 4.

REVISED TEXT

Criteria 15

15. A female subject is eligible to participate if she is of:

    - Non-childbearing potential defined in Section 6.10.2.1
    - Child-bearing potential as defined in Section 6.10.2.2, and agrees to use one of the contraception methods as described in Appendix 4~~, from the time of the screening pregnancy test until 7 months after the last dose of study medication.~~

Section 5.4. Withdrawal/Stopping Criteria

Rationale for change: Provides updated guidance for subjects who have discontinued combination treatment and are on fulvestrant monotherapy.

REVISED TEXT

Second paragraph last bullet point

- <u>discontinuation from combination treatment, or of GSK525762 with continuation on fulvestrant monotherapy for >6 months</u>

Twelfth paragraph onwards

Subjects who require permanent discontinuation of one of the study treatments in a given combination may continue on the other treatment until disease progression, withdrawal of consent, or unacceptable toxicity after discussion with Medical Monitor. <u>With the implementation of amendment 06, subjects who have permanently discontinued treatment with the combination, or of GSK525762 but have remained on fulvestrant monotherapy for >6 months should be discontinued from study.</u>

At the time of study completion, subjects with radiologically confirmed lack of disease progression (from Phase I and Phase II) who are still receiving GSK525762 and/or fulvestrant may continue treatment through a separate mechanism (e.g., roll-over protocol) to be determined at that time.

<u>Enrolment into the study is now closed. The study will conclude when the last subject has completed/discontinued study treatment and completed the end of treatment visit.</u>

Section 5.5 Subject and Study Completion

Rationale for change: These changes are based on the decision to close out the study and stop all new enrolment based on interim data failing to demonstrate meaningful clinical benefit in the proposed patient population. Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

REVISED TEXT

Third paragraph onwards

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. Enrolment into the study is now closed.

With the implementation of Amendment 06, specific assessments and collection of survival follow-up data will no longer be required. Please see Section 7.1 for further details. The study will conclude when the last subject has completed/discontinued study treatment and completed the end of treatment visit.

Section 6.1. Investigational Product and Other Study Treatment

Rationale for change: Provides clarification on clinical supply dosages available for the study.

REVISED TEXT

Investigational Product (Phase 1)				
Product name:	GSK525762C Tablets			Fulvestrant
Unit dose strength(s)/Dosage level(s):	5 mg	20 mg	25 mg	250 mg
Dosage form	Tablet	Tablet	Tablet	IM Injection
Manufacturer	GSK	GSK	GSK	AstraZeneca
Physical description:	White to slightly colored, round, biconvex tablet.			5-mL prefilled syringe containing 250 mg/5 mL fulvestrant. The solution for injection is a clear, colorless to yellow, viscous liquid.
Route/ Administration/ Duration:	**Oral;** see Time and Event Tables for schedule and administration timings			**IM**
Dosing instructions:	Dose with 240 mL liquid* and should be taken around the same time every day without regards to timing of meal (If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.)			Administer 500 mg intramuscularly into the buttocks slowly (1-2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29, and once monthly thereafter. There is a ±3-day dosing window for the fulvestrant.

NOTE: The Phase 1 formulation details are current at the time of protocol finalization and may be updated in other documents (e.g., SRM and/or informed consent form) without requiring protocol amendment. Phase 2 formulation details will be provided in an amendment.
*Subjects may take BET with 240 mL of liquid (other than orange, grapefruit, pomelo, or exotic citrus fruit juice). On serial PK days (W1D1 and W3D1), subjects must take BET with water only.

Section 6.2.2. Phase II

Rationale for change: These changes are based on the decision to close out the study and stop all new enrolment based on interim data failing to demonstrate meaningful clinical benefit in the proposed patient population.

REVISED TEXT

With implementation of amendment 06, Phase II of the study is terminated.

Section 7. STUDY ASSESSMENTS AND PROCEDURES

Rationale for change: These changes are based on the decision to close out the study and stop all new enrolment based on interim data failing to demonstrate meaningful clinical benefit in the proposed patient population. Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

REVISED TEXT

Third paragraph third bullet

- The timing and number of planned study assessments, may be altered during the course of the study based on newly available data to ensure appropriate monitoring. With the implementation of Amendment 06, specific assessments and collection of survival follow-up data will no longer be required. Please see Section 7.1 for further details.

Section 7.1. Time and Events Table

Rationale for change: These changes are based on the decision to close out the study and stop all new enrolment based on interim data failing to demonstrate meaningful clinical benefit in the proposed patient population. Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

REVISED TEXT

Table 4 Time and Events, Phase I

Procedure	SCR	Week 1		Week 2		Week 3		Week 4	Week 5	q4w	q8w	q8w	q12w	EOT[1]
		D1	D4	D1	D4	D1	D4	D1	D1	W9 to W49	W9 to W49	W49 and thereafter	W49 and thereafter	
Screening[2]														
Informed Consent	X													
Demography	X													
Medical History	X													
Inclusion/Exclusion Criteria	X													
Disease Characteristics	X													
Prior Therapy[3]	X													
Register Subject	X													
Safety														
Physical Exam[4]	X	X		X		X		X	X	X			X	X
ECOG PS[5]	X	X		X		X		X	X	X			X	X
12-lead ECGs[6]	X	X	X	X		X		X	X	X			X	X
Clinical Laboratory Assessments[7]	X	X	X	X	X	X	X	X	X	X				X
Echocardiogram or MUGA[8]	X								X	Week 13, 25, 37, 49			X	X
PRO-CTCAE[9]	X	~~X~~		~~X~~		~~X~~		~~X~~	~~X~~	~~X~~		~~X~~		~~X~~
Study Treatment														
Administer GSK525762[10]		Daily												

Procedure	SCR	Week 1		Week 2		Week 3		Week 4	Week 5	q4w	q8w	q8w	q12w	EOT[1]
		D1	D4	D1	D4	D1	D4	D1	D1	W9 to W49	W9 to W49	W49 and thereafter	W49 and thereafter	
Administer Fulvestrant[10]		X				X			X	X				
AE/SAE review		Continuous from signing of informed consent												
Concomitant medication review		Continuous from signing of informed consent												

Procedure	SCR	Week 1		Week 2		Week 3		Week 4	Week 5	q4w	q8w	q8w	q12w	EOT[1]
		D1	D4	D1	D4	D1	D4	D1	D1	W9 to W49	W9 to W49	W49 and thereafter	W49 and thereafter	
Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)														
PK blood samples[11]		~~PK~~				~~PK~~			~~O~~		~~X~~			
Tumor biopsy[12]	X						~~One sample, collected between W3D4 and W5D4, as close as possible to 3-6h post-GSK525762 dose~~							~~X~~[13]
Whole blood for exploratory analyses[13]	X							~~X~~						X
PGx blood sample[14]		X												
Efficacy														
CT chest/abdomen/~~pelvis~~[14]pelvis[15]	X										~~X~~	~~X~~		~~X~~
EORTC-QLQ-C30 & EORTC-QLQ-~~BR23~~[15]BR23[16]	X	~~X~~		~~X~~		~~X~~		~~X~~	~~X~~	~~X~~		~~X~~		~~X~~

1. Applies to subjects who withdraw for any reason prior to progression or who progress during study treatment. **With the implementation of amendment 06, following the EOT visit, subjects will no longer be contacted approximately every 3 months (± 14 days) to collect survival data.** ~~Following this visit, subjects will be contacted approximately every 3 months (± 14 days) to collect: survival status as of last date of contact and initiation of new anti-cancer therapy. Contact may be completed via a clinic visit, a telephone contact or an email~~.
2. Screening procedures should be performed as rapidly as possible within 28 days prior to Day 1 (first dose of study medication) to facilitate subject entry requirements. Clinical lab assessments should be completed within 14 days prior to dosing, and in case of abnormal test values, retesting may be performed if medically indicated and within 14 days prior to Day 1. Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging studies, etc.) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within 28 days prior to Day 1 (first dose of study medication) unless otherwise indicated: CT scans (within 30 days prior to Day 1) and ECHO/MUGA (within 35 days prior to Day 1).
3. Including dates of imaging and sizes of target lesion(s) used for RECIST 1.1 evaluation, if available.
4. Complete physical examination required at screening, Week (W)1 Day (D)1 (W1D1), and end of the treatment (EOT) visits. Limited examinations permitted at all other visits, as noted. Definition of complete and limited examinations may be found in Section 7.3.1. Post Week 49, assessments will be completed every 12 weeks.
5. Post Week 49, ECOG assessments will be completed every 12 weeks.
6. Triplicate ECGs should be performed at screening. All other timepoints can be single ECGs prior to dosing and evaluated for abnormality prior to administration of dose. Post Week 49, assessments will be completed every 12 weeks. Triplicate ECGs to be performed as clinically indicated, based upon abnormal findings.
7. Refer to Table 5 for details of clinical safety labs and timing of collection
8. Whatever scanning modality is used at screening should be maintained for all subsequent scans. An assessment is not performed at W9. Beginning at W13, scans will be performed once every 12 weeks.

9. **With the implementation of amendment 06, the PRO-CTCAE will no longer be collected.** ~~Patient Reported Outcomes Version of the Common a Terminology Criteria for Adverse Events (PRO-CTCAE) Item Library (Version 1.0). Post Week 49, assessments will be completed every 8 weeks~~.
10. Drugs should be administered as described in Section 6.1. Visits where fulvestrant is administered will be considered drug dispensing days. There is a ±3 day window for fulvestrant dosing. On PK collection days in Week 1 and Week 3, subjects should abstain from food from 8 h prior until 2 h after dose as described in Section 6.10.1. Post Week 49, fulvestrant will continue to be administered every 4 weeks. Refer to the SRM for further details.
11. **With the implementation of amendment 06, PK samples will no longer be collected.** ~~"PK" = serial PK days. Sample collections should be obtained at the following timepoints: Pre-dose, 30 m ± 5 m, 1 h ± 10 m, 3 h ± 30 m. "O" = sample collections to be obtained pre-dose, 0.5-1h post-dose, and an optional sample 4-8h post-dose. "X" = sample collections to be obtained pre-dose as well as 0.5-1h post-dose (note that routine PK is no longer required once the subject has been on study for 26 weeks). Pre-dose samples will be split to obtain a PK sample for fulvestrant analysis. Refer to the SRM for further details.~~
12. **With the implementation of amendment 06, tumor biopsies will no longer be collected, and the EOT tumor biopsy will no longer be collected.** ~~Mandatory Screening tumor biopsy specimen is required for all subjects; within 28 days prior to first study dose as described in Section 7.5.1. . Subjects providing an optional on-treatment fresh tumor biopsy, whether they have had a dose interruption of GSK525762 or not, must have received at least 4 consecutive doses of GSK525762 prior to the collection of the tissue. If the post-dose biopsy is not performed during this timeframe due to lab abnormalities or subject status, it should be performed at the next agreed upon visit with the medical monitor after subject recovery. Fresh biopsies should be paired with plasma samples for PK, collected as close as possible to biopsy (ideally within 1 h). Subjects must have a platelet count of ≥75,000/mm^3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy, or any other planned surgical procedure. Refer to the SRM for further details.~~
13. **With the implementation of amendment 06, whole blood for exploratory analyses will no longer be collected.** ~~A tumor biopsy at the end of treatment is optional, but strongly encouraged when clinically feasible.~~
14. **With the implementation of amendment 06, if a PGx sample has not yet been collected, collection will no longer be required.** ~~CT should be performed with oral and intravenous (IV) contrast. CT required at screening. Any potential CR or PR should be confirmed as described in Appendix 7. EOT disease assessment is not required if reason for discontinuing therapy was progressive disease and prior assessment was within 14 days of EOT visit. Subjects with contraindication to **contrast-enhanced computed tomography (CT)** or MRI may have imaging performed as described in Section 7.2.1.~~
15. **With the implementation of amendment 06, contrast-enhanced computed tomography (CT) scan data will no longer be required for disease assessment.** ~~European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core-30 and Breast 23 measures. Post Week 49, assessments will be completed every 8 weeks.~~
16. **With the implementation of amendment 06, EORTC questionnaires will no longer be collected.**

~~Table 6 Time and Events, Phase II~~

~~Procedure~~	~~SCR~~	~~Week 1~~		~~Week 2~~	~~Week 3~~	~~Week 4~~	~~Week 5~~	~~q4w~~	~~q8w~~	~~q8w~~	~~q12w~~	~~EOT[1]~~
		~~D1~~	~~D4~~	~~D1~~	~~D1~~	~~D1~~	~~D1~~	~~W9 to W49~~	~~W9 to W49~~	~~W49 and thereafter~~	~~W49 and thereafter~~	
~~**Screening[2]**~~												
~~Informed Consent~~	~~X~~											
~~Demography~~	~~X~~											
~~Medical History~~	~~X~~											

Procedure	SCR	Week 1		Week 2	Week 3	Week 4	Week 5	q4w	q8w	q8w	q12w	EOT[1]
		D1	D4	D1	D1	D1	D1	W9 to W49	W9 to W49	W49 and thereafter	W49 and thereafter	
Inclusion/Exclusion Criteria	X											
Disease Characteristics	X											
Prior Therapy[3]	X											
Register Subject	X											
Safety												
Physical Exam[4]	X	X		X	X	X	X	X			X	X
ECOG PS[5]	X	X		X	X	X	X	X			X	X
12-lead ECGs[6]	X	X	X	X	X	X	X	X			X	X
Clinical Laboratory Assessments[7]	X	X	X	X	X	X	X	X				X
Echocardiogram or MUGA[8]	X						X	Week 13, 25, 37, 49			X	X
PRO-CTCAE[9]	X	X		X	X	X	X	X		X		X
Study Treatment												
Administer GSK525762[10]		Daily										
Administer Fulvestrant[10]		X			X		X	X				
AE/SAE review		Continuous from signing of informed consent										
Concomitant medication review		Continuous from signing of informed consent										
Pharmacokinetics (PK), Translational Studies & Pharmacogenomics (PGx)												
PK blood samples[11]		O					O		X			
Tumor biopsy[12]	X											X[13]
Whole blood for exploratory analyses	X					X						X
PGx blood sample		X										
Efficacy												
CT chest/abdomen/pelvis[14]	X								X	X		X
EORTC-QLQ-C30 & EORTC-QLQ-BR23[15]	X	X		X	X	X	X	X		X		X

1. Applies to subjects who withdraw for any reason prior to progression or who progress during study treatment. Following this visit, subjects will be contacted approximately every 3 months (± 14 days) to collect: survival status as of last date of contact and initiation of new anti-cancer therapy. Contact may be completed via a clinic visit, a telephone contact or an

Procedure	SCR	Week 1		Week 2	Week 3	Week 4	Week 5	q4w	q8w	q8w	q12w	EOT[1]
		D1	D4	D1	D1	D1	D1	W9 to W49	W9 to W49	W49 and thereafter	W49 and thereafter	

email.

2. Screening procedures should be performed as rapidly as possible within 28 days prior to Day 1 (first dose of study medication) to facilitate subject entry requirements. Clinical lab assessments should be completed within 14 days prior to dosing, and in case of abnormal test values, retesting may be performed if medically indicated and within 14 days prior to Day 1. Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging studies, etc.) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within 28 days prior to Day 1 (first dose of study medication) unless otherwise indicated: CT scans (within 30 days prior to Day 1) and ECHO/MUGA (within 35 days prior to Day 1).
3. Including dates of imaging and sizes of target lesion(s) used for RECIST 1.1 evaluation, if available.
4. Complete physical examination required at screening, Week (W)1 Day (D)1 (W1D1), and end of the treatment (EOT) visits. Limited examinations permitted at all other visits, as noted. Definition of complete and limited examinations may be found in Section 7.3.1. Post Week 49, assessments will be completed every 12 weeks.
5. Post Week 49, ECOG assessments will be completed every 12 weeks.
6. Triplicate ECGs should be performed at screening. All other timepoints can be single ECGs prior to dosing and evaluated for abnormality prior to administration of dose. Post Week 49, assessments will be completed every 12 weeks. Triplicate ECGs to be performed as clinically indicated, based upon abnormal findings.
7. Refer to Table 7 for details of clinical safety labs and timing of collection
8. Whatever scanning modality is used at screening should be maintained for all subsequent scans. An assessment is not performed at W9. Beginning at W13, scans will be performed once every 12 weeks.
9. Patient Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Item Library (Version 1.0). Post Week 49, assessments will be completed every 8 weeks.
10. Drugs should be administered as described in Section 6.1. Visits where fulvestrant is administered will be considered drug dispensing days. There is a ±3 day window for the fulvestrant dosing. Post Week 49, fulvestrant will continue to be administered every 4 weeks. Refer to the SRM for further details.
11. "O" – sample collections to be obtained pre-dose, 0.5-1h post dose, and an optional sample 4-8h post dose. "X" – sample collections to be obtained pre-dose as well as 0.5-1h post-dose (note that routine PK is no longer required once the subject has been on study for 26 weeks). Pre-dose samples will be split to obtain a PK sample for fulvestrant analysis only for subjects who are receiving fulvestrant. Refer to the SRM for further details.
12. Screening tumor biopsy specimen is required for all subjects;the fresh specimen must be provided within 28 days prior to first study dose. It is acceptable to collect tumor biopsy specimen within the screening period. A sample collected within 3 months of first dose is also acceptable only if it was collected after the last anticancer treatment.– Refer to Section 7.2.1 and to the SRM for further details. Subjects must have a platelet count of ≥75,000/mm3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy, or any other planned surgical procedure.
13. Tumor biopsy at the end of treatment is optional, but strongly encouraged when clinically feasible
14. CT should be performed with oral and intravenous (IV) contrast. Any potential CR or PR should be confirmed as described in Appendix 7. EOT disease assessment is not required if reason for discontinuing therapy was progressive disease and prior assessment was within 14 days of EOT visit. Subjects with contraindication to contrast-enhanced computed tomography (CT) or MRI may have imaging performed as described in Section 7.2.1.
15. European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core 30 and Breast 23 measures. Post Week 49, assessments will be completed every 8 weeks.

Table 7 Time and Events, Phase 2 Laboratory Assessments

	SCR[1]	Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 11	q4w	q12w	EOT
		D1	D 4	D1	D1	D1	D1	D1	D1	D1	D1	D1	W13 and after	W49 and after	
Clinical chemistry	X	X	X	X	X	X	X		X		X	X	X	X	X
Hematology	X	X	X	X	X	X	X		X		X	X	X	X	X
Liver chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Troponin, N-terminal pro-B-Type natriuretic peptide (NT-proBNP)	X	X	X	X	X	X	X		X		X	X	X	X	X
Coagulation	X	X	X	X	X	X	X		X		X	X	X	X	X
Factor VII Assay[2]	X				X		X								
Fasting blood glucose	X	X	X	X	X	X	X		X		X	X	X	X	X
HbA1c	X						X		X		X	X	X	X	X
Fasting lipids	X						X		X		X	X	X	X	X
Thyroid (Thyroid stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4))[3]	X						X		X		X	X	X	X	X
Pancreatic	X	X		X	X	X	X		X		X	X	X	X	X
Urinalysis	X	X		X	X	X	X		X		X	X	X	X	X
HIV, Hepatitis B surface antigen (HBsAg), Hepatitis C Virus (HCV) Antibody	X														
FSH/Estradiol[4]	X														
Pregnancy test[5]	X	X			X		X		X		X	X	X		X

1. ~~Although strongly preferred, lab results for HBA1c, fasting lipids, TSH/T3/T4, and pancreatic enzymes are not required prior to dosing.~~
2. ~~Also perform if PT or INR are ≥1.5XULN, or in case of bleeding event~~
3. ~~TSH testing is mandatory. T4 testing is only required if TSH is abnormal. T3 testing is required when clinically applicable (if both TSH and T4 are abnormal).~~
4. ~~Only required at screening for pre- and peri-menopausal subjects~~
5. ~~Serum pregnancy test within 7 days prior to first dose; urine or serum test thereafter~~

Section 7.2.2. Visit Windows

Rationale for change: These changes are based on the decision to close out the study and stop all new enrolment based on interim data failing to demonstrate meaningful clinical benefit in the proposed patient population. Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

REVISED TEXT

First paragraph added

With the implementation of amendment 06, specific assessments and collection of survival follow-up data will no longer be required. Please see Section 7.1 for further details.

Section 7.3.3. Cardiac Safety

Rationale for change: Specific assessments, for purposes of the study, are being removed. Transfer of data to a central reader, for purposes of the study, is no longer required.

REVISED TEXT

7.3.3.1. Electrocardiograms

Last paragraph

ECG data ~~will~~may be transferred to a central facility for collection. Any central data may be reviewed by an independent central reviewer for retrospective analysis. With the implementation of amendment 06, transfer of ECG data to a central facility is no longer required.

7.3.3.2. Echocardiogram or Multigated Acquisition Scan

Second paragraph

Scan data may be transferred and reviewed by an independent cardiologist. Instructions for submission of qualifying scans are provided in the SRM. With the implementation of amendment 06, transfer of scan data for independent cardiologist review is no longer required.

Section 7.4. Pharmacokinetics

Rationale for change: Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

REVISED TEXT

First paragraph and second paragraph first sentence

With the implementation of amendment 06, PK samples will no longer be collected.

Blood samples for pharmacokinetic (PK) analysis of fulvestrant and GSK525762 (including relevant metabolite[s]) will be collected at the time points indicated in Table 4 ~~and Table 6.~~

Section 7.5. Pharmacodynamics

Rationale for change: Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

REVISED TEXT

With the implementation of amendment 06, tumor samples will no longer be collected.

Section 7.6. Evaluation of Anti-Cancer Activity

Rationale for change: Specific assessments, for purposes of the study, are being removed. Transfer of data to a central reader, for purposes of the study, is no longer required.

REVISED TEXT

First Paragraph

With the implementation of amendment 06, CT scan data will no longer be required for disease assessment. See the Time and Events Table (Section 7.1) for the updated schedule of assessments.

Fifth Paragraph

The baseline disease assessment will be completed within 30 days prior to the first dose of GSK525762 and fulvestrant, then approximately every 8 weeks thereafter and at the final study visit. ~~See the Time and Events Table (Section 7.1) for the schedule of assessments of anti-cancer activity.~~

Section 7.7.2. Tumor Tissue

Rationale for change: Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

REVISED TEXT

With the implementation of amendment 06, tumor samples will no longer be collected.

Section 7.7.3. Circulating cell free DNA/RNA Analysis

Rationale for change: Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

REVISED TEXT

With the implementation of amendment 06, blood samples will no longer be collected.

Section 7.8. Genetics

Rationale for change: Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

REVISED TEXT

With the implementation of amendment 06, if a subject has consented for PGx research but the sample has yet to be collected, this will no longer be required.

Section 7.9. Value Evidence and Outcomes

Rationale for change: Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

REVISED TEXT

7.9.1. PRO-CTCAE

With the implementation of amendment 06, the PRO-CTCAE will no longer be completed.

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

7.9.2. PRO-CTCAE EORTC-QLQ-C30 & EORTC-QLQ-BR23

With the implementation of amendment 06, the EORTC questionnaires will no longer be completed.

The effect of GSK525762 and fulvestrant, when given in combination, on symptoms and quality of life will be assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life questionnaires. Both the EORTC-QLQ-C30 (version 3) core questionnaire and the EORTC-QLQ-BR23 disease-specific modules will be administered.

Section 9 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

Rationale for change: These changes are based on the decision to close out the study and stop all new enrolment based on interim data failing to demonstrate meaningful clinical benefit in the proposed patient population. Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden. Any changes to the planned analyses for the study will be addressed in the Reporting Analysis Plan (RAP).

REVISED TEXT

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. Enrolment into the study is now closed as interim data failed to demonstrate meaningful clinical benefit in this patient population.

With the implementation of Amendment 06, specific assessments and collection of survival follow-up data will no longer be required. Please see Section 7.1 for further details. The study will conclude when the last subject has completed/discontinued study treatment and completed the end of treatment visit. There will be no Phase II.

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

Section 12.4.1. Contraception Guidance

Rationale for change: Updates to contraceptive measures required for study participants, based upon January 2020 updates to the fulvestrant Summary of Product Characteristics have been added to Appendix 4, Section 12.4.1.

REVISED TEXT

Note: Hormonal methods of contraception are not permitted since the efficacy of these methods in combination with GSK525762 has not been assessed. LHRH-acting agents alone are not considered an adequate form of contraception. GSK525762 has been shown to effect female reproductive systems in animals, therefore women of childbearing potential should adhere to this contraceptive guidance whilst on study and for 7 months after cessation of treatment with GSK525762, to be in line with GSK525762 guidance. **Effective January 13, 2020, the EU fulvestrant Summary of Product Characteristics was updated to include effective contraceptive use for women of childbearing potential for 24 months post last dose. Please consult the local fulvestrant prescribing information to ensure subjects are using effective forms of contraception for the appropriate length of time required after stopping treatment with fulvestrant.**

Section 12.11. Appendix 11: Genetic Research

Rationale for change: Specific assessments that are no longer required, due to the status of the study, are being removed to minimize patient burden.

REVISED TEXT

Study Assessments and Procedures

Last paragraph

Subjects can request their sample to be destroyed at any time. With the implementation of amendment 06, if a subject has consented for genetic research but the sample has yet to be collected, this will no longer be required.