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

Title	:	Reporting and Analysis Plan for A Phase I/II Open-Label, Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of GSK525762 in Subjects with NUT Midline Carcinoma (NMC) and Other Cancers
Compound Number	:	GSK525762
Effective Date	:	20-SEP-2016

Description :

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol BET115521.
- This RAP is intended to describe the safety, efficacy and pharmacokinetic analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Part 1 Interim Analysis and Statistical Analysis Complete (SAC) deliverable.

Author's Name and Functional Area:

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1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	• The purpose of this reporting and analysis plan (RAP) is to describe the planned analyses and output to be included in the Study Report for Protocol BET115521. This RAP is intended to describe the safety and efficacy analyses required for the study. This document will be provided to the study team members to convey the content of interim analysis and the Statistical Analysis Complete (SAC) deliverables.
Protocol	• This RAP is based on the protocol amendment 6 [(Dated: 19/JUN/2015) of study BET115521(GSK Document Number. : 2011N118599_06] and eCRF Version 14.0
Primary Objective	• To determine the safety, tolerability and maximum tolerated dose (MTD) of GSK525762 in subjects 16 years or older following Once Daily (QD) and/or BID dosing schedules. • To evaluate the clinical activity of GSK525762 in NMC and other solid tumors. • To evaluate, after single dose administration, the relative bioavailability of the GSK525762 besylate tablet compared to the amorphous free-base tablet, the effect of high-fat high-calorie meal on the bioavailability of the besylate tablet and the dose proportionality of two doses of GSK525762 administered as the besylate tablets.
Primary Endpoint	• 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 determine the MTD in subjects 16 years or older • Assess overall response rate (ORR) by RECIST 1.1 in NMC and other solid tumors. • Pharmacokinetic (PK) parameter values for GSK525762 following single oral administration as amorphous free-base or besylate tablet
Study Design	• Part 1 of the study is a dose escalation phase to determine the maximum tolerated dose (MTD) and select a recommended dose for Part 2 or a recommended Phase 2 dose (RP2D) based on the safety, pharmacokinetic, and pharmacodynamic profiles observed after oral administration of GSK525762. Eligible subjects with NUT midline carcinoma (NMC), small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), colorectal cancer (CRC), neuroblastoma (NB), castration resistant prostate cancer (CRPC), triple negative breast cancer (TNBC), estrogen receptor positive (ER positive) breast cancer, and any other MYCN-amplified solid tumor will be enrolled in the dosing cohorts until a maximum tolerated dose (MTD) is established. Subjects with NMC will also be enrolled in a pharmacodynamic dose expansion cohort during Part 1. Subjects may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent. • Part 1 besylate sub-study will explore the relative bioavailability, food effect and

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• All subjects enrolled in Part 1 QD dosing have had at least two post-baseline disease assessments or progressed or died or withdrawn from the study.

• All subjects enrolled in Part 1 BID dosing have had at least two post-baseline disease assessments or progressed or died or withdrawn from the study

During Part 2 (Expansion Cohort), regular futility analyses of response data will be conducted in order to determine whether the futility criteria for stopping have been met. The study will not be stopped early for positive response based on success criteria.

• For each expansion cohort, after the initial evaluable10 subjects have enrolled at the RP2D dose, response data will be reviewed on an ongoing and the cohort may be stopped for lack of evidence of efficacy (i.e. futility).

Final analyses will be carried-out at the time when 70% of all Part 2 subjects have progressed or died following the DBF (data base frozen) for Part 1 and DBF (data</td></tr>
</table>

Overview	Key Elements of the RAP
	base frozen) for Part 2 after all the data queries have been resolved.
Analysis Populations	• All Evaluable Subjects : This population will consist of all subjects that who have at least two post-dose disease assessment and been exposed to study drug for at least 28 days or have progressed or have died or have withdrawn from the study due to any reason. • All Treated Subjects : This population will consist of all subjects that received at least one dose of study treatment • PK Concentration Population : This population will consist of all subjects in the All Treated Subject Population for whom a blood sample for pharmacokinetics is obtained and analyzed • PK Parameter Population: This population will consist of all subjects in the PK Concentration Population for whom a PK parameter has been obtained • Besylate Sub-Study PK Parameter Population: This population will consist of all subjects in the PK Parameter Population who participated in the besylate sub-study. Any PK parameters obtained from a treatment that deviates from the assigned treatment won't be included in the primary relative bioavailability, food effect, or dose proportionality analyses • PD Population : This population will consist of subjects in the All Treated Subjects Population for whom a sample was obtained and analyzed for biomarkers
Hypothesis	No formal statistical hypotheses will be tested in Part 1. Analysis will be descriptive and exploratory. The primary goal of Part 2 is to demonstrate a clinically meaningful response, defined as follows: • NMC: this will be determined by testing the null hypothesis that the response rate is ≤5%, with about 80% power when the true response rate is 20%. • Small cell lung cancer (SCLC) and Castrate-Resistant Prostate Cancer (CRPC): this will be determined by testing the null hypothesis that the response rate is ≤10%, with about 80% power when the true response rate is 30%. • ER+BC: this will be determined by testing the null hypothesis that the response rate is ≤15%, with about 80% power when the true response rate is 30%. • Triple Negative Breast Cancer (TNBC): this will be determined by testing the null hypothesis that the response rate is ≤10%, with about 80% power when the true response rate is 25%.
Primary Analyses	• Safety: The All-Treated Subjects population will be used for the reporting and analysis of safety data. Some safety data may also be summarized separately by age, race, gender or other factors as needed. Summaries on extent of exposure, Adverse Events, clinical laboratory test results, vital signs, ECG ,

Overview	Key Elements of the RAP
	LVEF and liver events will be provided. • Efficacy: This study employs response criteria from RECIST version 1.1. The Overall Response Rate (ORR) is defined as the percentage of subjects achieving a confirmed Complete Response (CR) or Partial Response (PR) from the start of treatment until disease progression or the start of new anti-cancer therapy. Summaries of ORR by dose and tumor types will be provided. • PK analysis: The pharmacokinetic (PK) analyses will be based on the PK Concentration, PK Parameter and Besylate Sub-Study PK Parameter populations, unless otherwise specified.
Secondary Analyses	The secondary efficacy analyses on PFS (Progression Free Survival), OS (Overall Survival), DOR (Duration of Response), and TTR (Time to Response) will be based on the All Treated Subjects population, unless otherwise specified.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 7 (Dated: 10/MAR/2016).

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To determine the safety, tolerability and maximum tolerated dose (MTD) of GSK525762 in subjects 16 years or older following Once Daily (QD) and/or BID dosing schedules.	• 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 determine the MTD in subjects 16 years or older
• To evaluate the clinical activity of GSK525762 in NMC and other solid tumors.	• Assess overall response rate (RR) by RECIST 1.1 in NMC and other solid tumors.
• To evaluate, after single dose administration, the relative bioavailability of the GSK525762 besylate tablet compared to the amorphous free-base tablet, the effect of high-fat high-calorie meal on the bioavailability of the besylate tablet and the dose proportionality of two doses of GSK525762 administered as the besylate tablets.	• Pharmacokinetic (PK) parameter values for GSK525762 following single oral administration as amorphous free-base or besylate tablet
Secondary Objectives	**Secondary Endpoints**
• To characterize the pharmacokinetics (PK) of GSK525762 in subjects 16 years or older following QD and/or BID dosing schedules.	• PK parameter values for GSK525762 following single and repeat-dose oral administration in subjects 16 years or older
• To evaluate cardiac safety, including the potential for QT duration corrected for heart rate by Fridericia's formula (QTcF) changes with GSK525762 and to assess PK/QTcF relationship following QD and/or BID dosing schedules.	• Changes in cardiac safety including QTcF following single and repeat-dose oral administration GSK525762.

Objectives	Endpoints
• To evaluate the exposure response (pharmacokinetic/pharmacodynamic [PK/PD]) relationship between GSK525762 and safety and efficacy parameters following QD and/or BID dosing schedules.	
• To evaluate the effect of treatment with GSK525762 on tumor growth and survival.	• Progression free survival (PFS), time to response, duration of response, overall survival (OS), and exploratory analysis for antitumor response by various imaging modalities.
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the effect of GSK525762 on tumor biology	• Dose related changes in markers of cell proliferation and/or cell differentiation in tumor and/or surrogate tissue
• Correlation of GSK525762 exposure to changes in PD markers in tumor and/or surrogate tissue	• Dose related changes in transcription of genes and/or changes in expression of proteins regulated by BRD proteins in tumor and/or surrogate tissue
• To identify potential indicators of sensitivity or response to GSK525762.	• PK/PD parameter values for exposure response (by RECIST and 18FDG-PET [if data allows]) relationship between GSK525762 exposure and QTcF, troponin and tumor response following single and repeat-dose oral administration.
• To evaluate systemic and ex vivo on-target BET inhibitory effects.	• Changes from baseline and dose/response relationship in ex vivo Lipopolysaccharide (LPS) induced cytokines including Interleukin 6 (IL-6) in whole blood and systemic cytokines including IL-6.

2.3. Study Design

<table>
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<tr><td>Design Features</td><td>

Part 1 of the study is a dose escalation phase to determine the maximum tolerated dose (MTD) and select a recommended dose for Part 2 or a recommended Phase 2 dose (RP2D) based on the safety, pharmacokinetic, and pharmacodynamic profiles observed after oral administration of GSK525762. Eligible subjects with NUT midline carcinoma (NMC), small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), colorectal cancer (CRC), neuroblastoma (NB), castration resistant prostate cancer (CRPC), triple negative breast cancer (TNBC), estrogen receptor positive (ER positive) breast cancer, and any other MYCN-amplified solid tumor will be enrolled in the dosing cohorts until a maximum tolerated dose (MTD) is established. Subjects with NMC will also be enrolled in a pharmacodynamic dose expansion cohort during Part 1. Subjects may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent.
Part 1 besylate sub-study will explore the relative bioavailability, food effect and dose proportionality of besylate formulation. The sub-study will be conducted at active centers in the United States in subjects eligible for Part 1 at the MTD or a dose near the MTD or RP2D. This will be an open-label, randomized, single dose, four period, cross over sub-study to investigate the relative bioavailability of the besylate tablet compared to the amorphous free-base tablet, the effect of high-fat high-calorie meal on the bioavailability of the besylate tablet and the dose proportionality of two doses of GSK525762 administered as besylate tablets.

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Treatment D: 80mg QD besylate tablet, fed administration with FDA recommended high fat breakfast</td></tr>
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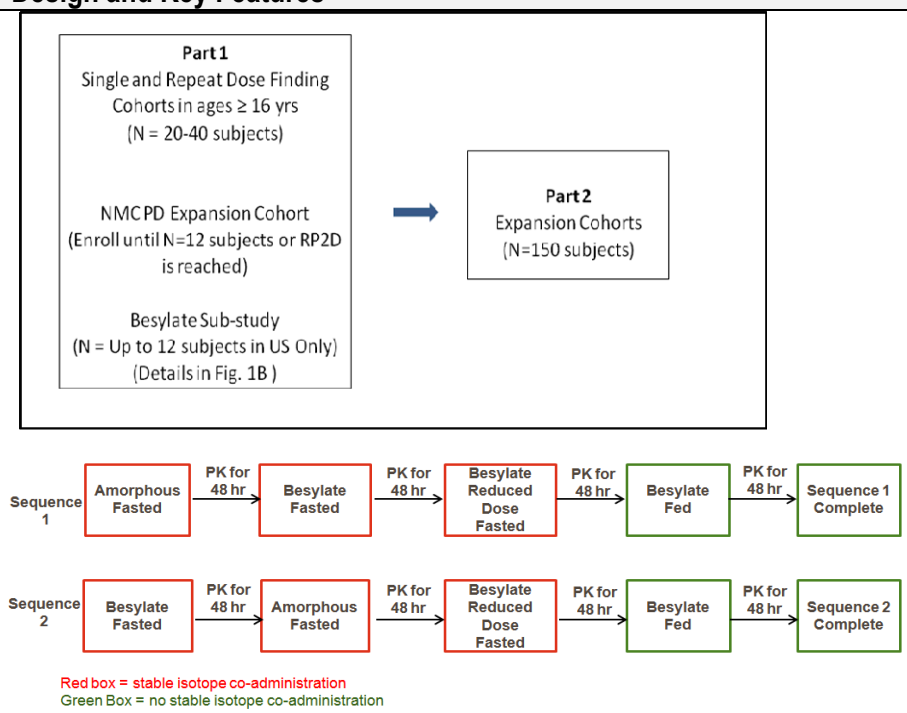
Part 2 is an expansion cohort planned to further explore clinical activity at the MTD in NMC, SCLC, CRPC, and TNBC and ER positive BC subjects.

</td></tr>
</table>

Overview of Study Design and Key Features	
	
Dosing	• Starting dose will be 2 mg, orally (tablets), once a day. Dose escalations will be performed in Part 1 and dose adjustments are allowed to address tolerability and safety issues. Alternate dosing schedules (BID or intermittent dosing) may be used based on PK and safety. • Subjects enrolled in the Part 1 dose escalation phase will be administered GSK525762 as an amorphous tablet. • Subjects enrolled in the Part 2 dose expansion phase will be administered GSK525762 as a besylate tablet.
Treatment Assignment	• This is a non-randomized open-label study.

Interim Analysis	• An interim analysis of the key parameters may be carried-out before the conclusion of the study. Full details of procedures and of the analyses planned at the interim analysis will be provided in the Reporting and Analysis Plan (RAP).
	• Two formal interim analyses will be performed for Part 1 of the study. The interim analysis on Part 1 will be conducted when
	  • All subjects enrolled in Part 1 QD dosing, including subjects enrolled in the Besylate Sub-Study, have had at least two post-baseline disease assessments or progressed or died or withdrawn from the study.
	  • All subjects enrolled in Part 1 BID dosing have had at least two post-baseline disease assessments or progressed or died or withdrawn from the study
	• An interim analysis of the Part 1 Besylate Sub-Study will be conducted

Overview of Study Design and Key Features	
	once the last patient enrolled in the Besylate Sub-Study completes their final respective PK blood draw for analysis. This interim analysis will not be a formal analysis, but will be used to determine if the besylate formulation is viable for use in Part 2. • Interim analysis on futility will be conducted during Part 2

2.4. Statistical Hypotheses

No formal statistical hypotheses will be tested in Part 1. Analysis will be descriptive and exploratory.

The primary goal of Part 2 is to demonstrate a clinically meaningful response, defined as follows:

- NMC: this will be determined by testing the null hypothesis that the response rate is ≤5%, with about 80% power when the true response rate is 20%.
- Small cell lung cancer (SCLC) and Castrate-Resistant Prostate Cancer (CRPC): this will be determined by testing the null hypothesis that the response rate is ≤10%, with about 80% power when the true response rate is 30%.
- ER+BC: this will be determined by testing the null hypothesis that the response rate is ≤15%, with about 80% power when the true response rate is 30%.
- Triple Negative Breast Cancer (TNBC): this will be determined by testing the null hypothesis that the response rate is ≤10%, with about 80% power when the true response rate is 25%.

3. PLANNED ANALYSES

3.1. Interim Analyses

An interim analysis of the key parameters may be carried-out before the conclusion of the study. Full details of procedures and of the analyses planned at the interim analysis are provided in this document (the RAP).

The study will not utilize an Independent Data Monitoring Committee (IDMC).

Dose escalation and stopping rules are guidelines for decision-making and the totality of the data will be considered by the team when making a decision. Clinical trial data used in these decisions will be in-stream data only; that is, the data will not necessarily be cleaned in advance of the formal interim analyses.

3.1.1. Part 1: Dose Escalation Phase

Two formal interim analyses will be performed for Part 1 of the study. The interim analysis on Part 1 will be conducted when

- All subjects enrolled in Part 1 QD dosing have had at least two post-baseline disease assessments or progressed or died or withdrawn from the study.
- All subjects enrolled in Part 1 BID dosing have had at least two post-baseline disease assessments or progressed or died or withdrawn from the study

An interim analysis of the Part 1 Besylate Sub-Study will be conducted once the last patient enrolled in the Besylate Sub-Study completes their final respective PK blood draw for analysis. This interim analysis will not be a formal analysis, but will be used to determine if the besylate formulation is viable for use in Part 2.

3.1.1.1. Description of the New Continual Reassessment Method

The N-CRM is a type of Bayesian adaptive dose-escalation scheme that estimates the parameters of a statistical model relating dose and toxicity, and is expected to locate the MTD efficiently while minimizing the number of subjects exposed to pharmacologically inactive or unsafe dose levels. The method is fully adaptive and makes use of all the toxicity information available at the time of each dose assignment. N-CRM estimates may be provided at dose escalation meetings as supportive material to the primary 3+3 dose escalation design.

The N-CRM estimates, for each potential dose, the (Bayesian) posterior probabilities that the DLT rate lies in each of four predefined toxicity ranges:

- A dose falls in the **Under-dosing** range if the rate of a DLT at the dose is in the interval [0%, 16%).
- A dose falls in the **Target** toxicity range if the rate of a DLT at the dose is in the interval [16%, 33%).
- A dose falls in the **Excessive** toxicity range if the rate of a DLT at the dose is in the interval [33%, 60%).
- A dose falls in the **Unacceptable** toxicity range if the rate of a DLT at the dose is in the interval [60%, 100%].

Additionally, the following over-dose constraints for the recommended dose will be maintained:

- The posterior probability of the DLT rate lying in the Excessive Toxicity or Unacceptable Toxicity range is 0.25 or less.
- The recommended dose is no more than 2 times that of the previous dose.

Note that a de-escalation recommendation is possible using this method. At the time of each dose-escalation decision, the dose with the highest posterior probability of lying in

the Target Toxicity range (subject to the given constraints) will be the model-recommended dose for the next cohort.

3.1.1.2. Prior Probability Distribution

Elicited prior probabilities of a DLT at each dose were used to determine the prior distribution of the parameters of an explicit logistic dose-toxicity model, namely

$$ln\left(p_d/(1-p_d)\right) = \alpha + \beta * ln\left(d/d_m\right),$$

where p_d is the probability of a DLT at dose d, and d_m is a reference dose.

The prior distribution of (α, ln(β)) will be assumed to be bivariate normal with means (standard deviations): E[α]=−1.4346 (1.829), E[ln(β)]=-0.0394 (0.4282), with correlation between α and ln(β) set to ρ=−0.25 and d_m=50mg.

3.1.1.3. Displays To Be Created For Dose Escalation Review

Evaluation of at least three subjects who have completed one cycle (28 days) of continuous daily dosing is required prior to determining the dose for the next cohort.

Review of preliminary data will be performed after completion of each dosing cohort in Part 1. Preliminary safety and study population data may include a demographic summary, adverse event (AE) summary, AE summary by maximum toxicity category, SAE listing, listing of AEs that are reported to be DLT's, and listing of AEs leading to dose modification. Spreadsheets containing relevant study data may also be supplied by the study data manager. Displays that may be created by the S&P team for these interim analyses are specified in the RAP spreadsheet

Further, after the first instance of a DLT and for each subsequent cohort, the recommended dose from the N-CRM method and updated posterior estimates of the probabilities of being in each dose-toxicity range may be provided. The Fixed and Adaptive Clinical Trial Simulator (FACTS) (Version 2.4 or higher) software from Tessella will be used to make N-CRM calculations.

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

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

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

3.1.2. Part 2: Expansion Phase

3.1.2.1. Stopping Rules for Futility

During Part 2 (Expansion Cohort), regular futility analyses of response data will be conducted in order to determine whether the futility criteria for stopping have been met. The study will not be stopped early for positive response based on success criteria.

For each expansion cohort, after the initial 10 evaluable subjects have enrolled at the RP2D dose, response data will be reviewed on an ongoing and the cohort may be stopped for lack of evidence of efficacy (i.e. futility).

For NMC, once 10 evaluable subjects have been enrolled into the expansion cohort to examine safety and efficacy, if 0 responses are observed, further enrolment into this cohort may be terminated. The number of observed confirmed responses will guide further enrolment according to the rules summarized in Figure 1. A maximum of 25 subjects in this cohort will be enrolled at the RP2D. All available data will be considered in making enrollment decisions.

Figure 1 Diagram of Stopping Rules for NMC Cohort Expansion

	Number of Responses			
Number of Subjects	**0**	**1**	**2**	**3**
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				

Figure 1: The shaded regions are the specific regions for stopping the study for futility. For instance, if there is no response in 10 subjects, then the predictive probability for success will be 10% or less (the futility criterion) and the study will be stopped.

For SCLC and CRPC, once 10 evaluable subjects have been enrolled in the cohort to examine safety and efficacy, if 0 responses are observed in either cohort, further enrolment into this cohort may be terminated. The number of observed confirmed responses will guide further enrolment according to the rules summarized in Figure 2. A maximum of 22 subjects will be enrolled at the RP2D. All available data will be considered in making enrollment decisions.

Figure 2 Diagram of Stopping Rules for SCLC and CRPC Cohort Expansion

	Number of Responses				
Number of Subjects	**0**	**1**	**2**	**3**	**4**
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					

Figure 2 Legend: The shaded regions are the specific regions for stopping the study for futility. For instance, if there is no response in 10 subjects, then the predictive probability for success will be 1% or less (the futility criterion) and the study will be stopped.

For TNBC, once 10 evaluable subjects have been enrolled in the cohort to examine safety and efficacy, if 0 responses are observed in the cohort, Part 2 of the trial may be terminated with no further enrolment in this cohort. The number of observed confirmed responses will guide further enrolment according to the rules summarized in Figure 3. A maximum of 37 subjects will be enrolled at the RP2D. All available data will be considered in making enrollment decisions.

Figure 3 Diagram of Stopping Rules for TNBC Cohort Expansion

	Number of Responses						
Number of Subjects	**0**	**1**	**2**	**3**	**4**	**5**	**6**
10	■						
11	■						
12	■						
13	■						
14	■						
15	■						
16	■						
17	■						
18	■						
19	■	■					
20	■	■					
21	■	■					
22	■	■					
23	■	■					
24	■	■					
25	■	■					
26	■	■	■				
27	■	■	■				
28	■	■	■				
29	■	■	■				
30	■	■	■	■			
31	■	■	■	■			
32	■	■	■	■			
33	■	■	■	■			
34	■	■	■	■	■		
35	■	■	■	■	■		
36	■	■	■	■	■	■	
37	■	■	■	■	■	■	■

Figure 3 Legend: The shaded regions are the specific regions for stopping the study for futility. For instance, if there is no response in 10 subjects, then the predictive probability for success will be 1% or less (the futility criterion) and the study will be stopped.

For ER+BC, once 10 evaluable subjects have been enrolled in each cohort to examine safety and efficacy, if 0 responses are observed, further enrolment into this cohort may be terminated. The number of observed confirmed responses will guide further enrolment according to the rules summarized in Figure 4. A maximum of 37 subjects per cohort will be enrolled at the RP2D. All available data will be considered in making enrollment decisions.

Figure 4 Diagram of Stopping Rules for ER+BC Cohort Expansion

	Number of Responses								
Number of Subjects	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
10	■								
11	■								
12	■								
13	■								
14	■								
15	■								
16	■	■							
17	■	■							
18	■	■							
19	■	■							
20	■	■							
21	■	■	■						
22	■	■	■						
23	■	■	■						
24	■	■	■						
25	■	■	■	■					
26	■	■	■	■					
27	■	■	■	■					
28	■	■	■	■					
29	■	■	■	■	■				
30	■	■	■	■	■				
31	■	■	■	■	■				
32	■	■	■	■	■	■			
33	■	■	■	■	■	■			
34	■	■	■	■	■	■	■		
35	■	■	■	■	■	■	■		
36	■	■	■	■	■	■	■	■	
37	■	■	■	■	■	■	■	■	■

Figure 4 Legend: The shaded regions are the specific regions for stopping the study for futility. For instance, if there is no response in 10 subjects, then the predictive probability for success will be 1% or less (the futility criterion) and the study will be stopped.

Because subjects enroll at different times, not all subjects will have had the same number of disease assessments at the time of each futility analysis. Subjects will be analyzed against the stopping criteria according to their order of enrolment/treatment. For example, the first futility assessment will be conducted after the 10th treated subject has completed a sufficient number of disease assessments to determine a confirmed response. The first 10 subjects treated will be included in the first futility assessment;.

Stopping boundaries are based on the number of confirmed responses out of the number of evaluated subjects; however, subjects who are ongoing in the trial at the time of a futility assessment with either a non-confirmed response or stable disease may eventually have a confirmed response. Therefore, the total number of subjects with confirmed or unconfirmed responses plus those who are ongoing with stable disease should be compared to the futility boundary to prevent stopping the trial for futility before all potential confirmed responses are fully realized. Because this represents the best-case scenario, if this count is still within the futility region, the study should be stopped.

3.1.2.2. Operating Characteristics of the Stopping Rules for Futility

The stopping rules in Figure 1, Figure 2, Figure 3 and Figure 4 are based on the methodology of Lee & Liu [Lee, 2008].

The following table describes for each disease cohort the null and alternative hypotheses that will be tested, maximum sample size and design characteristics. Each maximum sample size was calculated to ensure that at least 80% power and a maximum type 1 error rate of 10% is maintained.

Table 1 Diagram of Stopping Rules for Expansion Cohorts

	Null Hypothesis (H0) ORR	Alternative Hypothesis (Target) (Ha) ORR	Maximum Sample Size	Probability of stopping early for futility if H0 is true	Average Sample Size if H0 is true	Actual Type I Error Rate (%)	Actual Power (%)
NMC	5%	20%	25	0.891	14	8.8	80.2
CRPC	10%	30%	22	0.860	16	6.0	82.5
TNBC	10%	25%	37	0.876	23	6.4	81.7
ER+BC	15%	30%	37	0.855	25	8.7	80.3
SCLC	10%	30%	22	0.860	16	6.0	82.5

3.1.2.3. Displays To Be Created For Expansion Cohort Review

All Evaluable Subjects will be defined as the study population used for decision-making at the futility analysis. Because subjects treated at RP2D enrol at different times, not all subjects will have been on the study long enough to have single or multiple post-baseline disease assessments. Since disease assessments are to be completed every 4 weeks, for NMC, TNBC, ER+BC and SCLC cohorts, subjects who have at least two post-baseline radiological disease assessment and have been on study for at least 28 days or have progressed or have died or have permanently discontinued study treatment or withdrawn from the study treatment will be included in this population. For CRPC cohort, subjects who have at least two post-baseline radiological disease assessments or have had 13th week visit PSA test results or have progressed or died or permanently withdraw from the study treatment will be included in this population. This will be the population for summaries of response data for expansion cohort futility analysis.

All Treated will be defined as the population of all subjects that have been treated with at least one dose of the study drug at the time of the futility analysis. This will be the population for listings of data and for summaries of safety data and will include subjects from both Part1 and Part2.

A listing of subject responses over time will be produced. The listing will show the responses observed at each disease assessment for each subject along with the best confirmed and unconfirmed response. To be assigned a status of confirmed PR or confirmed CR, a confirmatory disease assessment should be performed no less than four weeks (28 days) after the criteria for response are first met. The definition of ongoing with stable disease is for subjects with Stable Disease as the best overall response and still on treatment at the time of futility analysis. The study population for this display will be All Treated population. A listing of Investigator-Assessed Target Lesion Assessments for ongoing with stable disease subjects will also be provided.

A listing of subject status and best overall response will be provided using the All Treated Subjects Population. This listing will be sorted by date of first dose and will show whether or not each subject is ongoing study treatment, whether the subject has had at least twopost-baseline radiological disease assessment, whether the subject is evaluable for the futility analysis, and best confirmed and unconfirmed response.

Summaries of confirmed best response will be provided so that the study team can compare the study data to the stopping rules for futility and to the success rules. Summaries of unconfirmed best response and will also be provided. The population for these displays will be All Evaluable Subjects.

If data allow, Summary of Kaplan-Meier Estimates of Progression Free Survival and the corresponding listings will be provided.

The total number of subjects with confirmed or unconfirmed responses or who are ongoing with stable disease should be compared to the futility boundary to prevent stopping the trial for futility before confirmed responses are fully realized. If this count is within the futility region, the study may be stopped based on the totality of the data. The purpose of including ongoing subjects with stable disease in this count is to avoid

incorrectly stopping the study early when responses of ongoing subjects have not been fully realized.

As always, these rules are guidelines for decision-making and the totality of the data will be considered by the team when making a decision to stop the study.

Table 2 Examples of Documentation of Recommendation from Futility Analysis During Part 2 (Expansion Cohort)

Example 1:

Number of Subjects (All Treated Subjects):	20
Number of Evaluable Subjects:	18
Futility Region:	1 or less
Number With Confirmed Response:	1
Number With Unconfirmed Response:	1
Number Ongoing with Stable Disease:	1
Recommendation:	Continue

Note: Compare (Number With Confirmed Response + Number Ongoing with Unconfirmed Response & SD) to Futility Region.

Example 2:

Number of Subjects (All Treated Subjects):	20
Number of Evaluable Subjects:	18
Futility Region:	1 or less
Number With Confirmed Response:	0
Number With Unconfirmed Response:	0
Number Ongoing with Stable Disease:	1
Recommendation:	Stop

Note: Compare (Number With Confirmed Response + Number Ongoing with Unconfirmed Response & SD) to Futility Region.

3.2. Final Analyses

Final analyses will be carried-out at the time when 70% of all Part 2 subjects have progressed or died following the DBF (data base frozen) for Part 1 and DBF (data base frozen) for Part 2 after all the data queries have been resolved.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Evaluable Subjects	• This population will consist of all subjects that who have at least two post-dose disease assessment and been exposed to study drug for at least 28 days or have progressed or have died or have withdrawn from the study due to any reason.	• Dose Expansion futility analyses

Population	Definition / Criteria	Analyses Evaluated
All Treated Subjects (Safety and Clinical Activity)	• This population will consist of all subjects that received at least one dose of study treatment	• Clinical Activity • Safety
PK Concentration Population	• This population will consist of all subjects in the All Treated Subject Population for whom a blood sample for pharmacokinetics is obtained and analyzed	• PK concentration
PK Parameter Population	• This population will consist of all subjects in the PK Concentration Population for whom a PK parameter has been obtained	• PK parameters
Besylate Sub-Study PK Parameter Population	• This population will consist of all subjects in the PK Parameter Population who participated in the besylate sub-study. Any PK parameters obtained from a treatment that deviates from the assigned treatment won't be included in the primary relative bioavailability, food effect, or dose proportionality analyses	• Besylate sub-study PK parameters
PD Population	• This population will consist of subjects in the All Treated Subjects Population for whom a sample was obtained and analyzed for biomarkers	• Plasma cytokines • LPS stimulated cytokines • Gene expression

NOTES :

- Please refer to Appendix 11: List of Data Displays which details the population to be used for each displays being generated.

4.1. Protocol Deviations

- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.
- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
    - Data will be reviewed prior to freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured in the protocol deviations dataset.
    - This dataset will be the basis for the summaries and listings of protocol deviations.
- A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 3 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 3 Overview of Appendices

Section	Component
13.4	Appendix 4: Data Display Standards & Handling Conventions
13.5	Appendix 5: Derived and Transformed Data
13.6	Appendix 6: Premature Withdrawals & Handling of Missing Data
13.7	Appendix 7: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the All Treated Subjects population, unless otherwise specified.

Table 4 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 4 Overview of Planned Study Population Analyses

Endpoint / Parameter	Data Displays Generated		
	Table	Figure	Listing
Disposition	Y		Y
Analysis Populations	Y		Y
Protocol Deviations	Y		Y
Demographics	Y		Y
Race	Y		Y
Disease Burden	Y		Y
Substance Use	Y		Y
Current/Past Medical Conditions	Y		Y
Disease Characteristics at Initial Diagnosis	Y		Y
Disease Characteristics at Screening	Y		Y
Metastatic Disease at Screening	Y		Y
Prior Anti-Cancer Therapy	Y		Y
Prior Cancer-Related Surgical Procedures	Y		Y
Concomitant Medications	Y		Y

NOTES :

- Y = Yes display generated.

6.1.1. Disposition of Subjects

A summary of the number of subjects in each of the dosing groups/cohorts will be provided. A listing of subjects excluded from analysis populations will also be provided.

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

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

6.1.2. Protocol Deviations

All protocol deviations will be summarized and listed and will include inclusion and exclusion deviations as well as other deviations.

6.1.3. Demographic and Baseline Characteristics

The demographic characteristics (e.g. age, race, ethnicity, sex, baseline height, and baseline body weight will be summarized and listed. In addition, age will also be categorized and summarized by <18, 18-64, 65-74, and >74. The count and percentage will be computed for sex and ethnicity.

Race and racial combinations will be summarized and listed.

Disease history and characteristics (primary tumor type, lesion status, time since initial diagnosis in weeks, stage at initial diagnosis and screening, time since last progression in weeks) will be listed. Separate summaries of disease characteristics at initial diagnosis and screening will be provided. Medical conditions present at screening will be listed and will be summarized by past and current categories.

Substance use, including smoking history and alcohol use, will be summarized and listed.

Prior anti-cancer therapy will be coded using GSK Drug coding dictionary, then summarized by type of therapy and listed. A listing of prior anti-cancer therapy will show the relationship between Anatomical Therapeutic Chemical (ATC) Level 1, Ingredient, and verbatim text. A summary of the best response to the most recent prior anti-cancer therapy will be provided. A summary of the number of prior anti-cancer therapy regimens will also be produced.

Prior anti-cancer radiotherapy will be summarized and listed. Prior cancer-related surgeries will be summarized and listed.

Bromodomains (BRDs) are small protein domains, found in a variety of proteins, that recognize and bind to acetylated histone tails. The bromodomain extra-terminal (BET) family of bromodomain proteins includes the BRD3, BRD4 and BRDT [testes] proteins will be summarized and listed.

6.1.4. Treatment Compliance

A listing of planned and actual treatments will be produced.

In addition, summaries of study treatment exposure and dose modifications (e.g. number of dose reductions, number of dose interruptions) will further characterize compliance.

6.1.5. Concomitant Medications

Concomitant medications will be coded using GSK Drug coding dictionary, summarized, and listed. The summary of concomitant medications will show the number and percentage of subjects taking concomitant medications by Ingredient. Multi-ingredient products will be summarized by their separate ingredients rather than as a combination of

ingredients. ATC classification Level 1 (Body System) information will be included in the dataset created but will not appear on the listing or summary.

In the summary of concomitant medications, each subject is counted once within each unique ingredient. For example, if a subject takes Amoxycillin on two separate occasions, the subject is counted only once under the ingredient “Amoxycillin”.

In the summary of concomitant medications, the ingredients will be summarized by the base only, using CMBASECD and CMBASE.

Blood products or blood supportive care products will be summarized separately. The frequency and percentage of subjects using blood products and blood supportive care products after the start of study medication will be provided. Supporting listings will also be provided.

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

6.1.6. Subsequent Anti-Cancer Therapies

The number and percentage of subjects that received chemotherapy, immunotherapy, hormonal therapy, biologic therapy, radioactive therapy, small molecule targeted therapy, radiotherapy and cancer-specific surgery as post study treatment anti-cancer therapy will be summarized. Time from study treatment discontinuation to the first post study treatment anti-cancer therapy will also be included in this summary table.

Follow-up anti-cancer therapy will be coded using GSK Drug coding dictionary, then summarized by ingredient. A listing of the type of follow-up anti-cancer therapy received (chemotherapy, immunotherapy, hormonal therapy, biologic therapy, radioactive therapy, small molecule targeted therapy, radiotherapy and cancer-specific surgery and details of the anticancer therapy for each subject will be provided.

7. EFFICACY ANALYSES

7.1. Overview of Planned Efficacy Analyses

The primary efficacy analyses will be based on the All Treated Subjects population, unless otherwise specified, and all summaries and data listings will use treatment labels as specified in Section 13.4.1. All summaries will be presented by Cohort and Study Part and overall.

Table 5 provides an overview of the planned efficacy analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 5 Overview of Planned Efficacy Analyses

Endpoint / Parameter	Absolute						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
Tumor Assessments (Investigator accessed and independent radiologist-assessed)							
Target Lesions						Y	Y
Non-Target Lesions							Y
New Lesions							Y
Tumor Response (confirmed and unconfirmed)				Y		Y	Y
Time to Event							
Progression-Free Survival	Y			Y	Y		Y
Overall Survival	Y			Y	Y		Y
Time to Response	Y			Y			Y
Duration of Response	Y			Y			Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

Endpoint / Parameter	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Tumor Assessments														
Target Lesions							Y						Y	Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

7.2. Primary Efficacy Analyses

This study employs response criteria from RECIST version 1.1. The Overall Response Rate (ORR) is defined as the percentage of subjects achieving a confirmed Complete Response (CR) or Partial Response (PR) from the start of treatment until disease progression or the start of new anti-cancer therapy.

Subjects with Not Evaluable or missing response will be treated as non-responders; i.e. they will be included in the denominator when calculating the percentage.

For Part 1, anti-tumor activities will be evaluated based on clinical evidence and response criteria. If the data warrant, the response data will be summarized by dose level and tumor type.

The primary aim of Part 2 is to demonstrate clinically meaningful response rates in each of the disease cohorts separately.

Overall response rate is defined as the percentage of subjects who achieved CR or PR among subjects who received at least one dose of treatment. Overall response rate and the associated 2-sided 95% exact confidence limits will be provided separately for each disease cohort. Confirmed and unconfirmed response summaries will be provided.

7.3. Secondary Efficacy Analyses

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

Secondary Efficacy Parameters	
Progression-Free Survival (PFS)	• PFS is defined as the interval of time (in months) between the date of first dose and the earlier of the date of disease progression and the date of death due to any cause.
Overall Survival (OS)	• OS is defined as the interval of time (in months) between the date of first dose and the date of death due to any cause.
Duration of Response (DOR)	• DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause among subjects who achieve a response (i.e. unconfirmed or confirmed CR or PR).
Time to Response (TTR)	• TTR is defined, for subjects with a confirmed CR or PR, as the time from first dose to the first documented evidence of CR or PR.

The date of documented disease progression will be defined as the first date of disease progression according to clinical or radiological assessment.

If there is no adequate baseline assessment, the subjects will be censored at their date of first dose day. Subjects without any adequate post-baseline tumor assessments will be censored at the date of first dose day.

Subjects who progressed or died after an extended period without adequate assessment will be censored at their date of last adequate assessment prior to progression or death even if subsequent information is available regarding progression or death. An adequate assessment is defined as an assessment where the response is CR, PR, or SD. The date of response at that assessment will be used for censoring. Censoring rules are defined in table below.

Subjects should not start subsequent anti-cancer therapy while on study. For subjects who receive subsequent anti-cancer therapy the following rules will apply:

- If the start date of the anti-cancer therapy is partial (i.e. either missing the day but has the month and year available or missing both day and month), the imputation rules described in Section 13.6.2.1. will be applied. No imputation will be made for completely missing dates.
- If anti-cancer therapy is started without documented disease progression or is started prior to documented disease progression, PFS will be censored at the date of the last adequate assessment that is no later than the date of initiation of anti-cancer therapy (i.e. if an assessment occurs on the same day as the start of new anti-cancer therapy the assessment will be used, as it will be assumed the assessment occurred prior to the administration of new anti-cancer therapy). The date of response at the last adequate assessment will be used as the censoring value.
- If a subject has only a baseline visit or does not have an adequate assessment that is no later than the date of initiation of anti-cancer therapy, PFS will be censored at the date of randomization.

If a subject has neither progressed nor died nor started new anti-cancer therapy, then PFS will be censored at the date of the last adequate assessment defined as an assessment where the Independent Reviewer/response is CR, PR, SD. The date of response will be used as the censoring date.

A summary of the assignments for progression and censoring dates for PFS are specified in the table below.

Censoring Rules		
Situation	**Date of Event (Progression/Death) or Censoring**	**Outcome: Event (Progression/Death) or Censoring**
No (or inadequate) baseline tumor assessments and the subject has not died (if the subject has died follow the rules for death indicted at the bottom of the table)	First Dose Date	Censored

Censoring Rules		
Situation	**Date of Event (Progression/Death) or Censoring**	**Outcome: Event (Progression/Death) or Censoring**
No post-baseline assessments and the subject has not died (if the subject has died follow the rules for death indicted at the bottom of the table)	First Dose Date	Censored
Progression documented between scheduled visits	Date of assessment of progression[1]	Event
No progression *(or death)*	Date of last 'adequate' assessment of response[2]	Censored
New anticancer treatment started *(prior to documented disease progression).*[3]	Date of last 'adequate' assessment of response[2] *(on or prior to starting anti-cancer therapy)*	Censored
Death before first PD assessment (or Death at baseline or prior to any adequate assessments)	Date of death	Event
Death between adequate assessment visits	Date of death	Event
Death or progression after more than one missed visit	Date of last 'adequate' assessment of response[2] *(prior to missed assessments)*	Censored

NOTES :

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

[2] An adequate assessment is defined as an assessment where the [Independent Reviewer/response is CR, PR, or SD.

[3] If PD and New anti-cancer therapy occur on the same day, assume the progression was documented first (e.g. outcome is progression and the date is the date of the assessment of progression). If anti-cancer therapy is started prior to any adequate assessments, censoring date should be the date of randomization.

PFS, OS, DOR and TTR will be graphically presented by dose and disease cohort using Kaplan-Meier plots if the data warrant.

If data permits, PFS, OS, DOR and TTR will be summarized descriptively by dose and disease cohort using Kaplan-Meier medians and quartiles. Only the subset of subjects who show a confirmed complete or partial tumor response will be included.

A sensitivity analysis will be performed using RECIST 1.1 alone for determining disease progression and RECIST 1.1 and clinical progression for determining disease progression. Additionally, separate analyses will be completed based on the investigator assessment of response and the independent radiological assessment of response. Subjects that were enrolled with multiple myeloma and neuroblastoma will not have an independent radiological assessment of response.

Secondary Statistical Analyses
Endpoint(s)
• PFS • OS • TTR • DOR
Method of Analysis
• Kaplan-Meier (if data warrant)

Sensitivity and Supportive Statistical Analyses
• Performed using RECIST 1.1 alone and RECIST 1.1 with clinical progression for assessment of response • Performed using investigator assessment of response and independent radiological assessment of response

8. SAFETY ANALYSES

8.1. Overview of Planned Analyses

The safety analyses will be based on the All Treated Subjects population, unless otherwise specified, and all summaries and data listings will use treatment labels as specified in Section 13.4.1. All summaries will be presented by Cohort and Study Part and overall.

Table 6 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 11: List of Data Displays.

Table 6 Overview of Planned Safety Analyses

Endpoint / Parameter	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Exposure	Y		Y	Y				
Adverse Events	Y			Y				
Lab Chemistry	Y	Y	Y	Y	Y			Y
Lab Hematology	Y			Y	Y			Y
Urinalysis	Y			Y				
Vital Signs	Y			Y	Y	Y		Y
ECG	Y	Y		Y	Y	Y		Y
ECOG Performance Status	Y			Y	Y			Y
LVEF	Y			Y	Y			Y
Liver Events	Y			Y				
Constitutional Symptoms	Y			Y				

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

8.2. Extent of Exposure

The number of doses administered of study treatment will be summarised with mean, median, standard deviation, minimum, and maximum. The duration of exposure to study treatment in weeks (from first day to last day of treatment plus) will also be summarised.

Dose intensity will be summarized using mean, median, standard deviation, minimum, and maximum.

Dose delays, reductions, escalations, and interruptions will be summarised by number of modifications and reasons for modifications. The summaries of dose modifications will be provided only if the data warrant. All the dose reductions, dose escalations, dose interruptions and missed doses and dose delays will be listed separately.

A horizontal bar graph of duration of treatment in days (from first day to last day of treatment plus 1 day) will be produced. This graph will display duration of treatment in days for each subject along with the treatment that the subject received and the subject's best response.

8.3. Adverse Events

An overview summary of AEs, including counts and percentages of subjects with any AE, AEs related to study treatment, AEs leading to permanent discontinuation of study treatment, AE leading to dose reductions, AEs leading to dose delays OR interruptions, SAEs, SAEs related to study treatment, fatal SAEs, and fatal SAEs related to study treatment will be produced. A summary of non-serious AEs that occurred in strictly 5% of the subjects or above will be provided (no rounding for the percentage will be used in terms of 5% threshold, e.g. events with 4.9% incidence rate should not be included in this table). The summary will be displayed by System Organ Class (SOC) and Preferred Term (PT).

The relationship between Medical Dictionary for Regulatory Affairs (MedDRA) SOC, PT, and Verbatim Text will be displayed.

Adverse events will be graded according to the CTCAE, Version 4.0. Adverse events will be coded to the PT level using the MedDRA dictionary.

A summary of number and percentage of subjects with any adverse events by maximum grade will be produced. AEs will be sorted by PT in descending order of total incidence. The summary will use the following algorithms for counting the subject:

- **Preferred term row**: Subjects experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.

- **Any event row**: Each subject with at least one adverse event will be counted only once at the maximum grade no matter how many events they have.

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

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

All AEs will be listed. Additionally, a listing of subject IDs for each individual AE will be produced.

A listing of adverse events recorded as dose-limiting toxicities will be provided. Additionally, a summary of the number of patients experiencing DLT's in each cohort will be provided.

8.3.1. Adverse Events of Special Interest

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of events. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional adverse events of special interest, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team agreements in place at the time of reporting.

The adverse events of special interest include but not limit to the following categories:

- Haematopoietic thrombocytopenia [NARROW] SMQ
- Haemorrhages [NARROW] SMQ
- Anaemias nonhaemolytic and marrow depression HLGT
- Torsade de pointes/QT prolongation [NARROW] SMQ,
- Drug related hepatic disorders - comprehensive search [NARROW] SMQ,
- Noninfectious diarrhoea [NARROW] SMQ
- Constipation PT
- Nausea and vomiting HLT
- Rash Preferred Terms

The events of special interest are listed in Section 13.5.3.

Summaries of the number and percentage of subjects with these events will be summarized by categories of AE of SI, preferred term and maximum toxicity grade in one table. The summary of event characteristics for each category of AE of SI will also be provided, including number of subjects with any event, number of events, number of subjects with any event that is serious, number of subjects with any event that is related to study treatment, the outcome of the event, maximum grade and the action taken for the event. The percentage will be calculated in two ways, one with number of subjects with event as the denominator and the other with total number of subjects as the denominator. The worst case approach will be applied at subject level for the event outcome and maximum grade, i.e. a subject will only be counted once as the worst case from all the events experienced by the subject. For action taken to a event, subject will be counted once under each action, e.g. if a subject has a event leading to both study treatment discontinuation and dose reduction, the subject will be counted once under both actions. For each category of AE of SI, the summary of onset and duration will also be provided. Time to onset (days) and duration of first occurrence (days) will be summarized. In addition to descriptive statistics (mean, median, min, max), time to onset will be summarized in categories of 1-14 days, 15-28 days and >28 days, and duration of first occurrence will be summarized in categories of 1-5 days, 6-10days, >10 days.

In addition, AEs of special interest will be listed separately.

8.3.2. Deaths and Serious Adverse Events

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

All SAEs will be tabulated based on the number and percentage of subjects who experienced the event. The summary table will be displayed in descending order of total incidence by PT only.

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

SAEs are included in the listing of all adverse events. Separate supportive listings with subject-level details will be generated for

- Fatal SAEs
- Non-Fatal SAEs.

8.3.3. Adverse Events Leading to Discontinuation of Study Treatment and/or Withdrawal from the Study and Other Significant Adverse Events

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

- AEs Leading to Discontinuation of Study Treatment
- AEs Leading to Withdrawal from the Study
- AEs Leading to Dose Interruptions
- AEs Leadings to Dose Reductions
- AEs Leading to Dose Increases

An AE leading to dose modification is an AE for which the action with respect to dosing is recorded as reduction or interruption of dose. Given the worst action is available; this AE will only be included in the summary table corresponding to the worst action. For example, AEs that lead to both a dose modification and a discontinuation of study treatment will only appear in the AEs leading to discontinuation of study treatment summary. All dose modifications due to AE will be listed in the listing.

8.4. Pregnancies

Any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. If subjects or subjects' partner become pregnant while on the study, the information will be included in the narratives and no separate table or listing will be produced.

8.5. Clinical Laboratory Evaluations

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

Serum Chemistry			
Blood urea nitrogen	Magnesium	aspartate aminotransferase	Total and direct bilirubin
Sodium	Potassium		Uric acid
Creatinine	Chloride	alanine aminotransferase	Albumin
Fasting Glucose	Total carbon dioxide	alkaline phosphatase	Total protein
Creatine phosphokinase	Ionized calcium	gamma-glutamyltransferase	Total calcium
Hematology			
Platelet count	*Automated White Blood Cell*		
Red blood cell count	*Differential:*		
White blood cell count (absolute)	Neutrophils (absolute)		
Hemoglobin	Lymphocytes (absolute)		
	Monocytes (absolute)		
	Eosinophils (absolute)		
	Basophils (absolute)		
Routine Urinalysis			
Specific gravity			
pH, glucose, protein, blood, and ketones by dipstick			
Microscopic examination (if blood or protein is abnormal)			
Other Tests			
Coagulation tests (prothrombin time, partial thromboplastin time, international normalized ratio, and fibrinogen)			
Pancreatic markers (amylase and lipase)			
Fasting Lipid panel (triglycerides and total cholesterol, LDL, HDL)			
C-Peptide			
Troponin (I or T at local laboratory, Troponin T at central laboratory]			
Insulin			
Hemoglobin A1C			
1,5 –Anhydroglucitol (1,5 AG)			
NT-proBNP			
Thyroid-stimulating hormone (TSH)			
Free Thyroxine 3 (Free T3)			
Free Thyroxine 4 (Free T4)			
Creatine kinase (CK)			
Creatine Kinase-MB (CK-MB)			
Testosterone for males (free and complete testosterone at prior to first dose, free testosterone after first dose)			
Pregnancy test for females (serum at screening, Urine or serum post dose)Cytokine samples (collected as part of Predose PK sample for plasma cytokines; may also be performed as clinically appropriate following fever)			

Laboratory grades will be reported using the Common Terminology Criteria for Adverse Events (CTCAE v4.0).

Summary of lab values and change from baseline by scheduled visits using mean, median, standard deviation, minimum, and maximum will be provided.

Summaries of lab data by maximum toxicity grade will be provided.

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

baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum grade of 3 and any increase to a maximum grade of 4. Missing baseline grade will be assumed as grade 0. In addition, the summary will include grade increase from baseline by scheduled visits. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g. sodium will be summarized as hyponatremia and hypernatremia.

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

Separate summary tables for hematology and chemistry laboratory tests will be produced.

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

Detailed derivation of baseline assessment is specified in Section 13.4.2.

Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of subjects with non-missing value at each particular visit.

8.5.1. Analyses of Liver Function Tests

Summaries of hepatobiliary laboratory events including possible Hy's law cases will be provided in addition to what has been described above.

Possible Hy's law cases are defined as any elevated (ALT≥3×ULN **and** total bilirubin≥2×ULN (with direct bilirubin ≥35% of total bilirubin, if direct bilirubin is measured)) **OR** (ALT ≥3×ULN **and** INR >1.5, if INR is measured). Note that INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants.

LFT patient profiles plots for subjects experiencing an ALT, AST or total bilirubin of toxicity grade 2 or above will be produced.

A plot of maximum total bilirubin versus maximum ALT will be generated. A trellis display of LFT shifts from baseline to maximum values will be provided. A matrix display of LFT results will also be produced.

A summary of liver re-challenges, adaptations and recovery will be provided. The re-challenge is defined as an ALT elevation, followed by treatment interruption and subsequently an ALT value of Grade 1 or below on or prior to re-starting study treatment,

where the ALT elevation means ALT is >3xULN and ≤3xULN at baseline. The adaptation is defined as an ALT elevation followed by an ALT assessment returning to baseline grade or below without any dose interruption between the ALT elevation and normalization. Recovery is defined as ALT Grade 1 or below for 2 consecutive visits or Grade 1 or below for one visit if subject discontinued and no data available.

8.6. Other Safety Measures

Unless otherwise specified, the denominator in the percentage calculation at each scheduled visit will be based on the number of subjects with non-missing value at each particular visit.

8.6.1. Vital Signs

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

Summaries of values of potential clinical concern with respect to the categories defined in Section 13.7.3. will be performed. These summaries will display the number and percentage of subjects with any PCI at each scheduled assessment time and for the worst case post-baseline.

8.6.2. Performance Status

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

A supporting listing will also be provided.

8.6.3. ECG

A summary of the number and percentage of subjects who had normal and abnormal (clinically significant and not clinically significant) ECG findings will be displayed by scheduled visits as well as for the worst case post-baseline.

Summaries of values of potential clinical concern with respect to the categories defined in Section 13.7.2. will be performed. These summaries will display the number and percentage of subjects with any PCI at each scheduled assessment time and for the worst case post-baseline.

In addition, ECG interval values will be also be summarized.

QTcF prolongation will be monitored throughout the study. Descriptive statistics and categorical analyses of QTcF and QTcF mean and individual profile plots will be generated periodically.

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

8.6.4. LVEF

Absolute change and relative percent change from baseline in LVEF will be summarized at each scheduled assessment time and for the worst case post-baseline. Only the post-baseline assessments that used the same method (i.e. ECHO) as the baseline assessments will be used to derive the change from baseline.

Summaries of values of potential clinical concern with respect to the categories defined in Section 13.7.4. will be performed. These summaries will display the number and percentage of subjects with any PCI at each scheduled assessment time and for the worst case post-baseline.

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

8.6.5. Liver Events

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

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

9. PHARMACOKINETIC ANALYSES

9.1. Overview of Planned Pharmacokinetic Analyses

The pharmacokinetic (PK) analyses will be based on the PK Concentration, PK Parameter and Besylate Sub-Study PK Parameter populations, unless otherwise specified.

Table 7 provides an overview of the planned analyses, with full details being presented in Appendix 11: List of Data Displays.

Table 7 Overview of Planned Pharmacokinetic Analyses

Endpoint / Paramete/ Display Type]	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
GSK525762 PK Parameters (Part 1 only)				Y	Y	Y	Y	Y		Y	Y	Y	Y	Y
GSK525762 PK Concentrations				Y	Y		Y				Y	Y	Y	Y
13C GSK525762 PK				Y		Y	Y	Y		Y	Y	Y	Y	Y

Endpoint / Paramete/ Display Type]	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Parameters (Besylate Sub-Study only)														
13C GSK525762 PK Concentrations (Besylate Sub-Study only)				Y	Y		Y				Y	Y	Y	Y

NOTES :

- T = Table, F = Figure, L = Listings, Y = Display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

9.2. Drug Concentration Measures

Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 13.4.3 Reporting Process & Standards).

9.3. Pharmacokinetic Parameters

9.3.1. Deriving Pharmacokinetic Parameters

- Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 13.4.3 Reporting Process & Standards).
- The pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using Phoenix WinNonlin software (versions 6.3).
- All calculations of non-compartmental parameters will be based on actual sampling times.
- Pharmacokinetic parameters described in Table 8 will be determined from the plasma concentration-time data, as data permits.

Table 8 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-∞)	Area under the concentration-time curve extrapolated to infinity will be calculated as: **AUC = AUC(0-t) + C(t) / lambda_z** This will be calculated for Week 1/Day 1 only
AUC(0-τ)	Area under the concentration-time curve from time zero to the predose of the next dose. For BID administration, AUC(0-24) will also be computed, as data permits.
Cmax	Maximum observed plasma concentration, determined directly from the concentration-time data. For BID administration, Cmax will be obtained after each administration, i.e. morning and evening administration, as data permits.

Parameter	Parameter Description
tmax	Time to reach Cmax, determined directly from the concentration-time data.
t½	Apparent terminal half-life will be calculated as: $t_{½} = \ln 2 / \lambda z$
λz	Apparent terminal phase elimination rate constant
Cτ	Trough concentration
CL/F	Apparent Clearance
V/F	Apparent Volume

NOTES:

- Additional parameters may be included as required.

To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) may be determined as the ratio of AUC(0-τ) on Week 3 AUC(0-τ) / Week 1 AUC(0-τ). Rs, the ratio of AUC(0-τ) on Week 3 AUC(0-τ) / Week 1 AUC(0-∞) may be calculated to assess time invariance.

GSK525762 concentrations will be determined in urine samples to determine urinary recovery of unchanged drug and renal clearance.

9.3.2. Statistical Analysis of Pharmacokinetic Parameters

Statistical analyses of the PK parameters data will be conducted by Oncology Statistics and Programming, GSK. Plasma concentration-time data will be listed by dose, age group, and summarized using descriptive statistics (n, mean, SD, median, minimum and maximum) by planned relative assessment time. Mean and/ or median values will be plotted over time. Individual plasma and urinary (if available) pharmacokinetic parameters values as well as a descriptive summary (mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation, CV% and 95% confidence interval of log-transformed parameters (if applicable)) by dose cohort and age group will be reported.

The following pharmacokinetic statistical analyses will only be performed, if sufficient data is available (i.e. if subjects have well defined plasma profiles).

9.3.2.1. Dose proportionality

Cmax and AUC (AUC(0-∞), single dose, and AUC(0-τ) or AUC(0-24), steady state), from Part 1 will be plotted as a function of the dose administered. Dose proportionality of AUC and Cmax for GSK525762 following single dose administration and AUC(0-τ) or AUC(0-24) and Cmax following repeat dose administration will be assessed graphically and using the power model as described below:

log (pharmacokinetic parameter) = a + b * log(dose)

where a is the intercept and b is the slope.

The power model will be fitted by restricted maximum likelihood (REML) using SAS Proc Mixed. Both the intercept and slope will be fitted as fixed effects. If there is

sufficient data, the model may also be fit with the intercept and/or slope as random effects depending on the ability of the model to converge and on estimation of variance-covariance matrix. The mean slope and corresponding 90% confidence interval will be estimated from the power model.

If data permit, a separate power model will be fit for PK parameters calculated from samples obtained following administration of BID dosing. For this dose proportionality analysis, Cmax for the morning dose and AUC(0-24) will be evaluated.

Part 1 Dose Proportionality Analysis
Endpoint(s)
• Cmax and AUC (AUC(0-∞), single dose, and AUC(0-τ) or AUC(0-24), steady state
Model Specification
• Proc Mixed code for dose proportionality analysis: PROC MIXED data=pkpar; BY paramcd; CLASS subjid; MODEL logpk = logdose / ddfm=kr; RANDOM subjid; RUN;
Model Checking & Diagnostics
• Refer to Appendix 9: Model Checking and Diagnostics for Statistical Analyses.

For Besylate Sub-Study analysis, the following power model will be fitted:

log (pharmacokinetic parameter) = a + b * log(dose) + c * log(C13PKparameter)

where a is the intercept and b is the slope.

The power model will be fitted by restricted maximum likelihood (REML) using SAS Proc Mixed. Both the intercept and slope and C13PKparameter will be fitted as fixed effects. The mean slope and corresponding 90% confidence interval will be estimated from the power model.

The besylate sub-study primary analysis will exclude data for a given period for a subject if the subject did not receive the correct dose during that period or the protocol-defined diet was not adhered to. A sensitivity analysis including data from all subjects based on actual treatment will also conducted.The analysis without C13PKparameters in the power model will also be provided as the sensitivity analysis.

Besylate Sub-Study Dose Proportionality Analysis
Endpoint(s)
• Cmax and (AUC(0-∞)
Model Specification
• Proc Mixed code for dose proportionality analysis in besylate sub-study: PROC MIXED data=pkpar; BY paramcd;

Besylate Sub-Study Dose Proportionality Analysis
CLASS subjid; MODEL logpk = logdose logc13pkpar / ddfm=kr; RANDOM subjid; RUN;
Model Checking & Diagnostics
• Refer to Appendix 9: Model Checking and Diagnostics for Statistical Analyses.

9.3.2.2. Relative bioavailability of the besylate salt tablet to the amorphous free base tablet (Besylate Sub-Study)

Pharmacokinetic (PK) parameters AUC(0-∞), AUC(0-t) and Cmax derived from treatments A2, B and C only will be $\log_e$-transformed and separately analyzed using a mixed-effects model with a fixed-effect term for treatments , and subject as a random effect. C13 PK parameter will be included in the model as a covariate. Point estimates and associated 90% CIs will be constructed for the differences between besylate salt (treatment B) and amorphous tables (treatment A2). The point estimates and their associated 90% CIs will then be back-transformed to provide point estimates and 90% CIs for the ratio of besylate salt/amorphous. Non-parametric methods such as the Hodges and Lehmann estimator will be used to estimate the median differences between the besylate salt tables and the amorphous tablets for tmax. An associated 90% CI for the median differences will be constructed. The besylate sub-study primary analysis will exclude data for a given period for a subject if the subject did not receive the correct dose or formulation during that period or the protocol-defined diet was not adhered to. A sensitivity analysis including data from all subjects based on actual treatment will also conducted with the exclusion of data collected after administration of the incorrect formulation in period 3 or 4.

Based on the US FDA guidance on relative bioavailability studies, two formulations will be considered bioequivalent if the 90% CI of the ratio for Cmax and AUC, based on log-transformed data, is within the 80 to 125% equivalence limit. Recommendation on the dose amount impact of a deviation from bioequivalence with the besylate salt will be based on the magnitude of the change.

The analysis without C13PKparameters in the mixed effects model will also be provided as the sensitivity analysis.

Relative Bioavailability of the Besylate Salt Tablet to the Amorphous Free Base Tablet Analysis (Besylate Sub-Study)
Endpoint(s)
• AUC(0-∞), AUC(0-t) and Cmax
Model Specification
• Only include treatments A2, B and C in the model. Proc Mixed code for relative bioavailability assessment: PROC MIXED data=pkpar; BY paramcd; CLASS subjid patrtcd;

Relative Bioavailability of the Besylate Salt Tablet to the Amorphous Free Base Tablet Analysis (Besylate Sub-Study)
MODEL logpk = patrtcd logc13pkpar / ddfm=kr; RANDOM subjid; ESTIMATE 'Besylate Salt – Amorphous' patrtcd -1 1 0 / alpha=0.1; LSMEANS patrtcd; RUN;
Model Checking & Diagnostics
• Refer to Appendix 9: Model Checking and Diagnostics for Statistical Analyses.

9.3.2.3. Food effect with besylate salt tablet (Besylate Sub-Study)

Pharmacokinetic (PK) parameters AUC(0-∞), AUC(0-t) and Cmax will be $\log_e$-transformed and separately analyzed using a mixed-effects model with a fixed-effect term for treatments, and subject as a random effect. Point estimates and associated 90% CIs will be constructed for the differences between fed (treatment D) and fasted state (treatment B). The point estimates and associated 90% CIs will then be back-transformed to provide point estimates and 90% CIs for the ratios of fed/fasted. Non-parametric methods such as the Hodges and Lehmann estimator will be used to estimate the median differences between the fed and fasted state for tmax. An associated 90% CI for the median differences will be constructed. The besylate sub-study primary analysis will exclude data for a given period for a subject if the subject did not receive the correct dose or formulation during that period or the protocol-defined diet was not adhered to. A sensitivity analysis including data from all subjects based on actual treatment will also conducted with the exclusion of data collected after administration of the incorrect formulation in period 3 or 4.

Food Effect with Besylate Salt Tablet Analysis (Besylate Sub-Study)
Endpoint(s)
• AUC(0-∞), AUC(0-t) and Cmax
Model Specification
• Proc Mixed code for food effect assessment: PROC MIXED data=pkpar; BY paramcd; CLASS subjid patrtcd; MODEL logpk = patrtcd / ddfm=kr; RANDOM subjid; ESTIMATE 'Fed – Fasted' patrtcd 0 -1 0 1 / alpha=0.1; LSMEANS patrtcd; RUN;
Model Checking & Diagnostics
• Refer to Appendix 9: Model Checking and Diagnostics for Statistical Analyses.

9.3.2.4. Relative Bioavailability of Solution to Besylate Salt Tablet (Besylate Sub-Study)

Dose normalized pharmacokinetic (PK) parameters AUC(0-∞), and Cmax will be $\log_e$-transformed and separately analyzed using a mixed-effects model with a fixed-effect term for PK type (C13 solution or besylate tablet), and subject as a random effect. Point estimates and associated 90% CIs will be constructed for the differences between solution and besylate tablet. The point estimates and associated 90% CIs will then be back-transformed to provide point estimates and 90% CIs for the ratios of solution to besylate tablet. Non-parametric methods such as the Hodges and Lehmann estimator will be used to estimate the median differences between solution and besylate tablet for tmax. An associated 90% CI for the median differences will be constructed.

The PK parameters for the C13 solution (6 mg administered) and the besylate tablet (80 mg administered fasted) will be dose normalized to 10 mg.

Relative Bioavailability of Solution to Besylate Salt Tablet Analysis (Besylate Sub-Study)
Endpoint(s)
• AUC(0-∞), and Cmax
Model Specification
• Proc Mixed code for relative bioavailability assessment: PROC MIXED data=pkpar; BY paramcd; CLASS subjid pktype; MODEL dnlogpk = pktype / ddfm=kr; RANDOM subjid; ESTIMATE 'Solution - Tablet ' pktype -1 1 / alpha=0.1; LSMEANS pktype; RUN;
Model Checking & Diagnostics
• Refer to Appendix 9: Model Checking and Diagnostics for Statistical Analyses.

9.4. Population Pharmacokinetic (PopPK) Analyses

- The primary goal of this analysis is to characterize the population pharmacokinetics of GSK525762 administered in subjects with solid tumors.
- A summary of the planned population pharmacokinetic analyses are outlined below:
  - Plasma concentration-time data from parts 1 and 2 will be combined and further analyzed using a population approach.
  - A nonlinear mixed effects model will be used to determine population pharmacokinetic parameters (absorption rate, Ka, apparent clearance, CL/F and volume of distribution, V/F) and summary exposure measures (Cmax, AUC and Cav = AUC/τ) and identify important covariates (e.g., age, weight, or disease related covariates).

10. PHARMACODYNAMIC ANALYSES

10.1. Overview of Planned Pharmacodynamic Analyses

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

11. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

- Observed (Part 1) or predicted concentrations (Part 2) will be combined with safety and efficacy pharmacodynamic measures of interest to examine potential exposure response relationships.
- The relationship between QTcF and concentration expressed as Cmax, Cav, and/or instantaneous time-matched concentration will be evaluated. A linear or non-linear mixed effects analysis of the relationship between QTcF adjusted for baseline and – concentration with a possible incorporation of time will be evaluated as a means of estimating QTcF effect in lieu of a thorough QT study.
- Other quantitative safety parameters, including platelet count, and biomarkers of interest will be plotted graphically against summary exposure measures (eg; Cmax, Ctrough, 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).

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13. APPENDICES

Section	Appendix
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 13.1	Appendix 1: Time and Events
Section 13.2	Appendix 2: Assessment Windows
Section 13.3	Appendix 3: Treatment States & Phases
Section 13.4	Appendix 4: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 13.5	Appendix 5: Derived and Transformed Data • General, Study Population & Safety • Pharmacokinetic • Pharmacodynamic and or Biomarkers
Section 13.6	Appendix 6: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 13.7	Appendix 7: Values of Potential Clinical Importance
Section 13.8	Appendix 8: Multicentre Studies • Laboratory Values • ECG • Vital Signs
Section 13.9	Appendix 9: Model Checking and Diagnostics for Statistical Analyses
Other RAP Appendices	
Section 13.10	Appendix 10: Abbreviations & Trade Marks
Section 13.11	Appendix 11: List of Data Displays
Section 13.12	Appendix 12: Example Mock Shells for Data Displays

13.1. Appendix 1: Time & Events

13.1.1. Protocol Defined Time & Events

See Protocol Section 5.

13.2. Appendix 2: Assessment Windows

No assessment windows will be applied.

13.3. Appendix 3: Treatment States and Phases

13.3.1. Treatment Phases

Adverse events, serious adverse events, death, laboratory data, vitals, ECG, echocardiogram (ECHO), Eastern Cooperative Oncology Group (ECOG) result, and and other safety domains will be assigned to the treatment phases defined below. Partial dates will be imputed into full dates, if applicable, for slotting data to the appropriate categories below (see Section 13.6.2). Flag variables (time in relation to study treatment) indicating the study time periods will be added to these datasets.

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

Treatment Phase	Definition
Pre-Therapy	Date ≤ Study Treatment Start Date
On-Therapy	Study Treatment Start Date < Date ≤ Study Treatment Stop Date

Some datasets include the first dose day as On-therapy and some exclude the first dose date as On-Therapy. The first dose day (Day 1) is considered pre-therapy for ECOG, ECG, vital signs, liver events, lab tests, cardiac scan, and other safety domains. The first dose day (Day 1) is considered to be On-therapy for adverse events and concomitant medications.

13.3.2. Treatment States

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

13.3.2.1. Treatment States for Disease Response Data

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

13.3.2.2. Treatment States for AE Data

Treatment State	Definition
Pre-Treatment	AE Start Date < Study Treatment Start Date
On-Treatment	If AE onset date is on or after treatment start date & on or before treatment stop date. Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date
Onset Time	• If Treatment Start Date > AE Onset Date = AE Onset Date - Treatment Start Date

Treatment State	Definition
Since 1st Dose (Days)	• If Treatment Start Date ≤ AE Onset Date = AE Onset Date - Treatment Start Date +1 • Missing otherwise.
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Drug-related	If relationship is marked 'YES' on [Inform/CRF OR value is missing].

NOTES:

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

13.4. Appendix 4: Data Display Standards & Handling Conventions

13.4.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Data Display	Order [1]
A	GSK525762 Active Dose	GSK525762 X mg (QD or BID)	5
A2	RP2D (or MTD) amorphous free-base tablet, fasted	A2	1
B	RP2D (or MTD) besylate tablet, fasted	B	2
C	half to one-third of RP2D (or MTD) besylate tablet, fasted	C	3
D	RP2D (or MTD) besylate tablet, fed	D	4

NOTES:

1. Order represents treatments being presented in TFL, as appropriate.

Treatment Group Descriptions			
Treatment	Data Display	Description	Order [1]
Part 1 QD dosing	2-16 mg QD	Combine lower dose cohorts 2mg, 4mg, 8mg, 16mg	1
	30 mg QD		2
	60 mg QD		3
	80 mg QD		4
	100 mg QD		5
	Total QD		6
Part 1 BID dosing	20 mg BID		8
	30 mg BID		9
	Total BID		10
Besylate Sub-Study	Besylate	Besylate Sub-Study subjects only	11
Part 2 Dose	75 mg QD	Besylate formula	12
Total	Total	All subjects combined	13

NOTES:

1. Order represents treatments being presented in TFL, as appropriate.

Cohort Descriptions		
Group Description	**Data Display**	**Order [1]**
NMC Cohort	NMC	1
CRPC Cohort	CRPC	2
TNBC Cohort	TNBC	3
ER+BC Cohort	ER+BC	4
SCLC Cohort	SCLC	5
Combined Cohorts	All Subjects	6

Study Part Descriptions		
Group Description	**Data Display**	**Order [1]**
Part 1: Dose Escalation Phase	Part 1: Dose Escalation Phase	1
Part 1: Besylate Sub-Study	Part 1: Besylate Sub-Study	2
Part 2: Expansion Phase	Part 2	3
Combined Study Parts	All Study Parts	4

13.4.2. Baseline Definition & Derivations

13.4.2.1. Baseline Definitions

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

For subjects who did not receive study treatment during the study, baseline will be defined as the latest, non-missing collected value.

For ECG analyses, subject level baseline is defined as the mean of triplicate baseline assessments.

13.4.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]

NOTES :

- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

13.4.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software be used.	
Reporting Area	
HARP Server	US1SALX00259
HARP Area	: Compound:GSK525762, Study:BET115521
QC Spreadsheet	: arprod\gsk525762\bet115521\.\documents
Analysis Datasets	
• Analysis datasets for Part 1 IAs will be created under IDSL standard • Analysis datasets will be created according to CDISC standards (SDTM IG Version X.X & AdaM IG Version X.X]. • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• RTF files will be generated for SAC and IA upon request.	

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: ○ 4.03 to 4.23: General Principles ○ 5.01 to 5.08: Principles Related to Data Listings ○ 6.01 to 6.11: Principles Related to Summary Tables ○ 7.01 to 7.13: Principles Related to Graphics
Formats
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time
• Reporting for tables, figures and formal statistical analyses : • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate. • Reporting for Data Listings: • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).

Reporting Standards	
• Unscheduled or unplanned readings will be presented within the subject's listings. • Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.	
Unscheduled Visits	
• Unscheduled visits will not be included in summary tables. • Unscheduled visits will be included in figures. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Reporting of Pharmacokinetic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 Assign zero to NQ values (Refer to GUI_51487 for further details)
Reporting of Pharmacokinetic Parameters	
Descriptive Summary Statistics (Log Transformed)	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of logged data and [between and or within] geometric coefficient of variation (CVb/w (%)) will be reported. [1] CV_b (%) = $\sqrt{}$ (exp(SD^2) - 1) * 100 (SD = SD of log transformed data) [2] CV_w (%) = $\sqrt{}$ (exp(MSE) - 1) * 100 (MSE = mean square error from mixed effect model of loge-transformed data).
Parameters Not Being Log Transformed	Tmax
Summary Tables	[The following PK parameters will not be summarised: "Insert PK parameters".]
Listings	[Additionally, include the first point, last point and number of points used in the determination of lambda_z for listings.]
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

13.5. Appendix 5: Derived and Transformed Data

13.5.1. General

Multiple Measurements at One Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two values within a time window the value closest to the target day for that window will be used. If values are the same distance from the target then the mean will be taken. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from study treatment start date:
  • Ref Date = Missing, then Study Day = Missing
  • Ref Date < Study Treatment Start Date, then Study Day = Ref Date – Study Treatment Start Date
  • Ref Data ≥ Study Treatment Start Date, then Study Day = Ref Date – (Study Treatment Start Date) + 1

13.5.2. Study Population

Demographics
Age

• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  ○ Any subject with a missing day will have this imputed as day '15'.
  ○ Any subject with a missing date and month will have this imputed as '30th June'.
• Birth date will be presented in listings as 'YYYY'.

Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)^2**

Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1** • Subjects who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. • The cumulative dose will be based on the formula: **Cumulative Dose = Sum of (Number of Days x Total Daily Dose)** • If there are any treatment breaks during the study, exposure data will be adjusted accordingly.

13.5.3. Safety

Adverse Events

AE'S OF Special Interest

- Drug eruption
- Fixed drug eruption
- Dermatitis allergic
- Exfoliative rash
- Eyelid rash
- Genital rash
- Mucocutaneous rash
- Nodular rash
- Paraneoplastic rash
- Perineal rash
- Rash
- Rash erytematous
- Rash follicular
- Rash generalised
- Rash macular
- Rash macula-papular
- Rash maculovesicular
- Rash morbilliform
- Toxic skin eruption
- Red man syndrome
- Dermatitis exfoliative
- Dermatitis exfoliative generalised
- Urticaria popular
- Urticaria physical
- Urticaria pigmentosa
- Urticaria vesiculosa
- Urticaria
- Urticaria vasculitis
- Rash popular
- Rash papulosquamous
- Rash pruritic
- Rash pustular
- Rash vesicular
- Vasculitic rash
- Vuvovaginal rash
- Parakeratosis
- Epidermal necrosis
- Acantholysis
- Transient acantholytic dermatosis
- Skin disorder
- Pain of skin
- Cutaneous contour deformity
- Peau d'orange
- Skin plaque
- Skin degenerative disorder
- Stevens-Johnson syndrome
- Skin reaction
- Dermatitis allergic
- Panniculitis
- Erythema induration
- Chronic actinic dermatitis
- Pruritus allergic
- Allergic respiratory symptom
- Drug hypersensitivity
- Erythma dyschromicum perstans
- Skin induration
- Excessive skin
- Skin discolouration
- Sca
- Dilated pores
- Skin fibrosis
- Sticky skin
- Scar pain
- Dermatosis
- Koebner phenomenom
- Skin fragility
- Skin discomfort
- Skin texture abnormal
- Fingerprint loss
- Skin odour abnormal
- Skin lesion
- Skin fissures
- Papule
- Dry skin
- Skin maceration
- Tubuculid
- Cutaneous calcification
- Skin swelling
- Skin tightness
- Skin warm
- Skin necrosis
- Macule
- Eosinophilic pustular

Adverse Events
AE'S OF Special Interest

- Dermatitis atopic
- Eczema herpeticum
- Skin sensitisation
- Erythema multiforme
- Toxic epidermal necrolysis
- Drug reaction with eosinophilia and systematic symptoms
- folliculitis
- Pathergy reaction

Laboratory Parameters

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

13.6. Appendix 6: Premature Withdrawals & Handling of Missing Data

13.6.1. Premature Withdrawals

Element	Reporting Detail

General	• In Part 1, a subject will be considered to have completed the study if
	  ○ they complete screening assessments, the 28-day DLT observation period, and the end-of-treatment follow-up visit,
	  ○ they progress or die while receiving study treatment, or
	  ○ are receiving ongoing study treatment at the time of the Sponsor's decision to close the study.
	• In Part 2, a subject will be considered to have completed the study if:
	  ○ they progressed or die while receiving study treatment, or
	  ○ are receiving ongoing study treatment at the time of the Sponsor's decision to close the study.
	• Withdrawn subjects may be replaced in the study.
	• All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

13.6.2. Handling of Missing Data

Element	Reporting Detail

General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument :
	  ○ These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table.
	  ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

13.6.2.1. Handling of Missing and Partial Dates

Imputed partial dates will not be used to derive study day, duration (e.g. duration of adverse events), or elapsed time variables. In addition, imputed dates are not used for deriving the last contact date in the overall survival analysis dataset.

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

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

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

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

blank: indicates that no imputation was done

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

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

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

Example of date variables:

XYZD_ – character date variable

XYZDT – numeric date variable

XYZDTFL – flag variable

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

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 3: Treatment States and Phases. ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied.
Anti-Cancer Therapy and Radiotherapy	• Completely missing start or end dates will remain missing, with no imputation applied. • If partial start date contains a year only set to January 1st. • If partial start date contains a month and year set to the 1st of the month. • No imputation for partial end dates will be performed.
Surgical Procedures	• No Imputation for completely missing dates • If partial date contains a year only set to January 1st. • If partial date contains a month and year set to the 1st of the month

Element	Reporting Detail

Concomitant Medication and Blood and Blood Supportive Products	• No Imputation for completely missing start or end dates
	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = January 1.
	• Else if study treatment start date is not missing:
	  ○ If year of start date = year of study treatment start date then
	  ▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1.
	  ▪ Else set start date = study treatment start date.
	  ○ Else set start date = January 1.
	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = 1st of month.
	• Else if study treatment start date is not missing:
	  ○ If month and year of start date = month and year of study treatment start date then
	  ▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month.
	  ▪ Else set start date = study treatment start date.
	  ○ Else set start date = 1st of month.
	• If partial end date contains year only, set end date = earliest of December 31 or date of last contact.
	• If partial end date contains month and year, set end date = earliest of last day of the month or date of last contact.

Time to Event and Response for Anti-Cancer Therapy Where applicable: Radiotherapy, Surgical Procedures	• Start dates for follow-up anti-cancer therapy, radiotherapy (where applicable), and surgical procedures (where applicable) will be temporarily imputed in order to define event and censoring rules for progression-free survival, response rate, or duration of response (i.e. start date for new anti-cancer therapy). Dates will only be imputed when a month and year are available but the day is missing. The imputed dates will not be stored on the anti-cancer therapy, radiotherapy, or surgical procedure datasets. The following rules will be used to impute the date when partial start dates are present on anti-cancer therapy radiotherapy, and/or surgical procedures datasets. • No Imputation for completely missing start dates • No imputation for missing start day and month (note the eCRF should only allow for missing day) • If partial start date falls in the same month as the last dose of study treatment, then assign to earlier of (date of last dose of study treatment+1, last day of month). • If partial start date falls in the same month as the subject's last assessment and the subject's last assessment is progressive disease (PD), then assign to earlier of (date of PD+1, last day of month). • If both rules above apply, then assign to latest of the 2 dates • Otherwise, impute missing day to the first of the month. • No imputation for partial end dates will be performed
Exposure End Dates for Subjects Who Are Still on Study at the Time of Analysis	• If exposure end date is missing, then assign exposure end date as the earliest of: the date of the data cutoff, the date of withdrawal from the study, or the death date. • The imputed exposure end date will be used to calculate cumulative dose and exposure duration. • The imputed exposure end date will be stored in the exposure analysis dataset and an exposure end date imputation flag variable will be derived indicating which exposure end date records are imputed.

Element	Reporting Detail
	• Imputed exposure end dates will also be stored on the study treatment end date variable. • For subjects who have missing end dates in their last exposure record because they are still on study treatment, the on-therapy indicator variables (time in relation to study treatment) are assigned to on-therapy for all records where the 'dataset'.'date' is after or on the study treatment start date.

13.7. Appendix 7: Values of Potential Clinical Importance

13.7.1. Laboratory Values

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

To identify laboratory values of potential clinical importance, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.0) will be used to assign grades to the relevant laboratory parameters. NCI-CTCAE v4.0 can be found at http://ctep.cancer.gov/reporting/ctc.html.

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

13.7.2. ECG

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

13.7.3. Vital Signs

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

13.7.4. Left Ventricular Ejection Fraction

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

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

13.8. Appendix 8: Multicenter Studies

13.8.1. Methods for Handling Centres

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

13.9. Appendix 9: Model Checking and Diagnostics for Statistical Analyses

Not applicable for this study.

13.10. Appendix 10 – Abbreviations & Trade Marks

13.10.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
IA	Interim Analysis
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
GUI	Guidance
LOC	Last Observation Carries Forward
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
GSK	GlaxoSmithKline

13.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
FACTs
SAS
WinNonlin

13.11. Appendix 11: List of Data Displays

13.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.0010 to 1.1200	
Efficacy	2.0010 to 2.0540	12.0010 to 12.0140
Safety	3.0010 to 3.3050	13.0010 to 13.0550
Pharmacokinetic	5.001041 to 5.0210	15.0010to 15.0090
Section	**Listings**	
ICH Listings	21.0010 to 25.0050	
Other Listings	21.0010 to 25.0050	

13.11.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided in Appendix 12: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Pharmacodynamic and / or Biomarker	PD_Fn	PD_Tn	PD_Ln
Pharmacokinetic / Pharmacodynamic	PKPD_Fn	PKPD_Tn	PK/PD_Ln

NOTES:

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

13.11.3. Deliverable [Priority]

Delivery [Priority] [1]	Description
IA QD [X]	Interim Analysis Statistical Analysis Complete for QD dosing
IA BID [X]	Interim Analysis Statistical Analysis Complete for BID dosing
IA Exp [X]	Interim Analysis for expansion cohort futility analysis
SAC [X]	Final Statistical Analysis Complete

NOTES:

1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort.

13.12. Appendix 12: Example Mock Shells for Data Displays

Example Non-Standard
Protocol: BET115521 Page 1 of 1
Population: All Treated Subjects (Data as of: 30MAY2013)
Table 1
Table of PSA response

Treatment: GSK525762

	xxmg (N=xx)
PSA Changes	
Decline>=50% from baseline (>=12week)	xx (xx%)
Decline>=30% from baseline (>=12week)	xx (xx%)
No significant PSA change[1]	xx (xx%)
PSA Progression	xx (xx%)
Not Evaluable[2]	xx (xx%)
Response Rate	
PSA >=50% reduction	xx (xx%)
95% Confidence Interval	(xx%, xx%)

1 Subjects who do not have decline>=30% from baseline (>=12week) or PSA progression
2 Subjects who do not have baseline PSA value or still on treatment but do not have ≥12 week visit PSA test results are treated as not evaluable

Example Non-Standard
Protocol: BET115521 Page 1 of 1
Population: All Treated Subjects (Data as of: 30MAY2013)
Listing 1
Listing of Subject Best Response for Interim Review by First Dose Date (Tumor type)

Treatment: GSK525762

Date of First Dose	Subject	Ongoing?	Measurable disease at baseline	At Least One Post-Baseline Assessment?	Evaluable for Interim Analysis?	Best Response (Confirmed)	Best Response (Unconfirmed)
01Apr2012	xxx	Yes	Yes	Yes	Yes	SD	CR
05May2012	xxx	Yes	Yes	Yes	Yes	SD	SD
06May2012	xxx	No	Yes	Yes	Yes	PR	PR
08Jan2013	xxx	No	Yes	Yes	Yes	SD	SD
08Mar2013	xxx	Yes	Yes	No	No		
08Apr2013	xxx	Yes	No	No	No	NE	NE

Response: CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease, NE= Not Evaluable.

Note to programmer: This display should be sorted by Date of First Dose

Example Non-Standard
Protocol: BET115521 Page 1 of 1
Population: All Treated Subjects (Data as of: 30MAY2013)
Listing 2
Listing of CRPC Subject PSA Response for Interim Review by First Dose Date

Treatment: GSK525762

Date of First Dose	Subject	Ongoing?	Had ≥12 week PSA Assessment?	Evaluable for Interim Analysis?	Maximum PSA Decline %	PSA Response
01Apr2012	xxx	Yes	Yes	Yes	85	Decline>=50% from baseline (>=12week)
05May2012	xxx	Yes	Yes	Yes	41	Decline>=30% from baseline (>=12week)
06May2012	xxx	No	Yes	Yes	No decline	PSA progression
09Jun2012	xxx	No	Yes	Yes	5	PSA progression
08Jan2013	xxx	No	Yes	Yes	10	No significant PSA change
08Mar2013	xxx	Yes	No	No	20	Not Evaluable
08Apr2013	xxx	Yes	No	No	No decline	Not Evaluable

Note to programmer: This display should be sorted by Date of First Dose