Statistical Analysis Plan

Study ID: 205801-003 (Sub Study 3)

Study Official Title: A Phase II, Randomized, Open-label Platform Trial Utilizing a Master Protocol to Study Novel Regimens Versus Standard of Care Treatment in NSCLC Participants

NCT ID: NCT06926673

Date of Document: 05-June-2024

Note: The Platform Trial 205801 comprises several arms, each individually registered on ClinicalTrials.Gov. This SAP document pertains specifically to Arms 4 and 5 of Sub-study 3. On the first page, there is a reference to a different NCT ID, which refers to the Master Record (NCT03739710), as the NCT ID for Sub-study 3 was not available when this SAP was being developed.

Information Type: Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: Phase II, Randomized, Open-label Platform Trial Utilizing a Master Protocol to Study Novel Regimens Versus Standard of Care Treatment in NSCLC Participants

The purpose of this SAP is to describe the planned final analysis and outputs for Arm 4 and Arm 5 in the Clinical Study Report (CSR) for 205801.

Study Number: 205801

Compound Number: GSK4428859A

Abbreviated Title: Ph2 Platform Trial of Novel Regimens vs. SoC in NSCLC (ENTREE)

Acronym: ENTRÉE Lung

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

Registry	ID
Clintrials.gov	NCT03739710

TABLE OF CONTENTS

LIST OF TABLES

VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	08 Mar 2021	04 (02-Feb-2021)	Not Applicable	Original version
SAP amendment 1	05 Jun 2024	10 (26-Apr-2023)	Analysis and reporting of Arms 4 and 5 have been added.	Protocol was amended to add new safety arms in part 1.

1. INTRODUCTION

The purpose of this SAP is to describe the planned final analysis and outputs for Arm 4 and Arm 5 in the Clinical Study Report (CSR) for 205801.

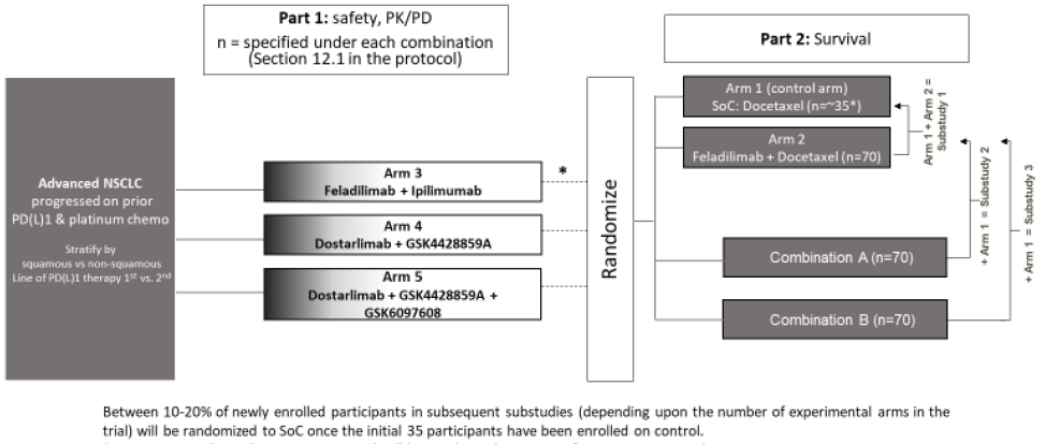
Additional detail with regards to data handling conventions and the specifications of data displays is provided in the Output and Programming Specification (OPS) document.

1.1. Objectives and Endpoints

Table 1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the safety and tolerability of novel regimen(s)	• AEs, SAEs, DLTs, changes in safety/laboratory assessment parameters, dose modifications
Secondary	
• To provide a preliminary evaluation of the efficacy of experimental regimen(s)	• Objective Response Rate (ORR) • Disease Control Rate (DCR)
• Characterize the pharmacokinetic properties of experimental regimen(s)	• PK parameters that include Cmax and Cmin for experimental regimen(s) (and investigational agent/s included in other arms), as data permit.
Exploratory	
CCI [redacted]	

Table 2 Overview of Study Design and Key Features

Overview of Study Design and Key Features	
	
Design Features	• This is a platform study with two parts: Part 1 and Part 2. • Part 1 of this open-label, platform trial is a non-randomized part based on safety and pharmacokinetics/pharmacodynamics (PK/PD) evaluation. Part 2 is a randomized, Phase II comparing the efficacy and safety of novel regimens with docetaxel as the SoC control arm (Arm 1). • Part 1 Arm 4 of this study will evaluate the safety of GSK4428859A (Anti- TIGIT) in combination with dostarlimab. Part 1 Arm 5 will evaluate GSK4428859A in combination with dostarlimab and GSK6097608 (Anti-CD96) • Additional treatment arms may be added via future protocol amendments, and ongoing treatment arms may be closed based on emerging safety information. This SAP will be updated accordingly.
Study intervention	• Dose escalation and safety will be evaluated based on mTPI design. • Experimental (combination) treatments will be administered at the indicated schedule with the maximum duration as specified in the protocol for each combination arm, or until disease progression as determined by RECIST 1.1, death, unacceptable toxicity, or other protocol-defined criteria are met.

Arm	Treatment Arm	Route of Administration	Dosing Frequency
Arm 4	CCI mg dostarlimab + CCI mg GSK4428859A	CCI [redacted]	

Overview of Study Design and Key Features				
			CCI mg dostarlimab + CCI mg GSK4428859A	CCI
			CCI mg dostarlimab + CCI mg GSK4428859A	
		Arm 5*	CCI mg dostarlimab + CCI mg GSK4428859A + CCI mg GSK6097608	CCI
			CCI mg dostarlimab + CCI mg GSK4428859A + CCI mg GSK6097608	
			CCI mg dostarlimab + CCI mg GSK4428859A + CCI mg GSK6097608	
		Arm 5 – PK/PD cohort (randomized)**	CCI mg dostarlimab + CCI mg GSK4428859A + highest tolerable GSK6097608 dose	
			CCI mg dostarlimab + CCI mg GSK4428859A + CCI mg GSK6097608	

* De-escalation to CCI mg CCI may be considered in accordance to the mTPI dose decision rules presented

** This is a randomized cohort where highest tolerable dose from arm 5 is randomized against CCI mg dostarlimab + CCI mg GSK4428859A + CCI mg GSK6097608

Study intervention Assignment	• In Arm 4, participants will be assigned to GSK4428859A at CCI mg, CCI mg, or CCI mg in combination with the fixed dostarlimab dose of CCI mg. Based on the mTPI dose escalation decision rules; once a dose is cleared, additional subjects may be added to cohorts for further safety evaluation. • For the safety evaluation in Arm 5, participants will be assigned to GSK6097608 at CCI mg, CCI mg, or CCI mg in combination with the fixed GSK4428859A dose of CCI mg and dostarlimab dose of CCI mg. Based on the mTPI dose escalation decision rules; once a dose is cleared, additional subjects may be added to cohorts for further safety evaluation. When evaluating PK/PD, participants will be randomly assigned to receive GSK6097608 at the highest tolerable dose or CCI mg in a 1:1 allocation ratio.

Overview of Study Design and Key Features	
Interim Analysis	• CCI [redacted] • Safety and exposure data may be periodically aggregated by treatment arms within clinical data review platforms (eg. Cockpit, JReview) or in outputs provided by statistical programmers to enable medical, safety review, or to support regulatory interactions.

2. STATISTICAL HYPOTHESES

The primary objective of Part 1 is to establish the safety and tolerability of the experimental combination regimen of each arm.

2.1. Multiplicity Adjustment

No multiplicity adjustment is needed for Part 1 analysis.

3. ANALYSIS SETS

Table 3 Analysis Sets

Analysis Set	Definition / Criteria	Applicable Arm(s) and/or Cohort(s)	Analyses Evaluated
Screened	• All participants who were screened for eligibility and signed the ICF.	• All arms	• Study Population
Safety	• All participants who received at least one dose of experimental regimen. Output will be based on actual treatment received.	• All arms	• Safety tables • Study Population
Intent-To-Treat (ITT)	• All participants who were randomized to treatment regardless of whether the participants actually received study treatment.	• Arm 5 Randomized PK/PD cohort	• Study Population • Efficacy • Safety Listings

Analysis Set	Definition / Criteria	Applicable Arm(s) and/or Cohort(s)	Analyses Evaluated
Enrolled	• All subjects that passed screening and were assigned treatment. Output will be based on assigned treatment.	• Arm 4 • Arm 5 dose escalation cohort	• Safety Listings • Study Population • Efficacy
Pharmacokinetic (PK)	• All participants in the safety population from whom at least one blood sample was obtained and analysed for PK concentration.	• All arms	• PK Concentration and PK parameters
DLT Evaluable	• All participants who take at least 1 dose of study intervention and are followed for the DLT observation period or are withdrawn within the DLT observation period due to meeting the DLT criteria and no resolution/recovery per dose modifications and toxicity management guidelines.	• Arm 4 • Arm 5 dose escalation • Arm 5 randomized PK/PD* **Note: participants enrolled in a PK/PD cohort at a previously cleared dose will not be included in the DLT evaluation population*	• DLT

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Which analysis sets will be used for specific analyses, tables, and listings are described in the above Analysis Sets table.

Confidence intervals will use 95% confidence levels unless otherwise specified.

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

See Section 12.1.5.13 of the protocol for the criteria for an interim CCI [redacted]

4.1.2. Baseline Definition

For all endpoints, including laboratory data, the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time (pre-dose/post-dose information) is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

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

4.2. Primary Endpoint(s) Analyses

The primary endpoints are DLT rate, and incidence of AEs, and SAEs. The analysis and reporting of AEs and SAEs are discussed in Section 4.5.2.

4.2.1. Definition of Endpoint(s)

A DLT is an AE that is flagged as a DLT in the CRF following the team's review, where the team concludes that the AE satisfies the DLT criteria in the Dose Limiting Toxicity section of the protocol, and the participant is DLT evaluable.

4.2.2. Main analytical approach

A summary of the number of patients experiencing DLTs will also be provided. Subject level data on adverse events recorded as DLTs during the determinative period will be available in RAPIDO.

These outputs will also be produced for CCI [redacted] if applicable.

4.3. Secondary Endpoint(s) Analyses

4.3.1. Key secondary endpoint(s)

The secondary endpoints in part 1 are, Objective Response Rate (ORR), Disease Control Rate (DCR) and PK parameters including Cmax and Cmin.

ORR is defined as the percentage of participants with a best overall confirmed Complete Response (CR) or Partial Response (PR) at any time as per RECIST1.1

DCR is defined as the percentage of participants with a confirmed CR + PR at any time, plus SD ≥ 12 weeks.

Best overall response (BOR) will be derived on investigator assessments of overall response at each visit recorded from the start of treatment until the criteria for progression are met (considering any requirement for confirmation when needed), or the date of initiation of new anti-cancer therapy (Note: This excludes palliative radiotherapy), or death date, whichever is earliest, as assessed by the investigator per RECIST 1.1.

For RECIST 1.1,

- To be assigned a status of confirmed CR/PR, a confirmatory disease assessment should be performed no less than 4 weeks (28 days) after the criteria for response are first met.
- Responses of CR/PR that do not meet the requirements of confirmed CR/PR are still eligible to be considered SD if it has met the SD criteria.
- For RECIST 1.1, to be assigned a status of SD, follow-up disease assessment(s) must have met the SD criteria at least once after the first dose at a minimum of 6 weeks ± 7 days (35 days) from baseline. If the minimum of 35 days for SD is not met, the best overall response will depend on the subsequent assessments. For example, if an assessment of PD follows the assessment of SD and SD does not meet the minimum 6-week requirement the best response will be PD. Alternatively, participants lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.
- If NE (Not Evaluable) is recorded in between initial and confirmatory CR or PR, then it can be disregarded to obtain the Best Response.
- A SD between an initial PR and confirmation PR can also be disregarded to obtain the Best Response of PR.

Table 4 Best Overall Response Criteria

Overall Response first timepoint	Overall Response subsequent timepoint	Best Overall Response
CR	CR	CR

CR	PR	SD provided minimum criteria for SD duration met, otherwise, PD
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD provided minimum criteria for SD duration met, otherwise, NE
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
SD	SD	SD provided minimum criteria for SD duration met, otherwise, NE
SD	PD	SD provided minimum criteria for SD duration met, otherwise, PD
SD	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

Derived Pharmacokinetic Parameters for study interventions will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of Phoenix WinNonlin.

All calculations of non-compartmental parameters will be based on actual sampling times.

Table 5 PK Parameters

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time 0 to the time of last quantifiable concentration will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
Cmax	Maximum observed plasma concentration, determined directly from the concentration-time data.
Cmin	Minimum observed concentration
Ctau	Pre-dose (trough) drug concentration, where tau is the end of the dosing interval

NOTES:
Additional parameters may be included as required, and will be specified in the OPS.

ORR

The number and percentage of participants with the BOR in the following response categories will be summarized: CR, PR. The corresponding exact 95% CI for ORR will also be provided. Participants with unknown or missing responses will be treated as non-responders, i.e., these participants will be included in the denominator when calculating percentages of response. A figure displaying maximum reduction in tumor size and listing of participant level responses will be generated. A listing of investigator assessed lesion assessments (RECIST 1.1 Criteria) will also be generated.

DCR

The number and percentage of participants with the BOR in the following response categories will be summarized: CR, PR, SD. The corresponding exact 95% CI for DCR will also be provided. Participants with unknown or missing responses will be treated as non-responders, i.e., these participants will be included in the denominator when calculating percentages of response.

Pharmacokinetic Summary Measures

Serum concentration data will be summarised separately for each of the study components of study treatment and dose levels. Corresponding listing of the serum concentration values will also be produced.

For each of these parameters, the following summary statistics will be calculated for each treatment and visit, if data permit, and presented separately: median, minimum, maximum, arithmetic mean, 95% confidence interval for the arithmetic mean, standard deviation, coefficient of variation (%CV = 100*(sqrt (exp(SD^2) - 1))) [NOTE: SD = SD of natural log (log_e) transformed data]), geometric mean, 95% confidence interval for the geometric mean and standard deviation of natural logarithmically transformed data.

All derived PK parameters will be listed and summarized.

A table summarizing the arithmetic mean, geometric mean, CV%, and range for day 1 pre-dose dostarlimab will be generated. Only participants with quantifiable pre-dose dostarlimab will be included in the calculations for this table.

The concentration-time data and PK parameter values should not be rounded-off prior to statistical analysis. The number of decimal places used in the reporting in primary tables of PK parameters obtained directly from concentration data will be dictated by the analytical methodology. However, PK parameter values will generally be reported in text and data listings (both parameter and concentration listings) to a number of decimal places consistent with 3 significant figures for the lowest value for that parameter, unless the original data for that parameter is reported to less precision throughout (in which case the precision of the original data will be used). The usual standards for precision of summary statistics will then be applied.

4.4. Exploratory Endpoint(s) Analyses

CCI

[redacted]

4.5. Safety Analyses

The safety tables will be based on the Safety Analysis Set and listings will be based on Enrolled Set, unless otherwise specified.

4.5.1. Extent of Exposure

Extent of exposure to experimental arm data will be presented by component and summarized, including number of cycles, dose intensity, relative dose intensity, actual cumulative dose, and actual and expected duration of exposure. Summary statistics will be produced, as well as a listing of exposure to different monotherapies. The Safety population will be used.

Extent of exposure data will be calculated based on the following formula:

Expected duration of exposure (i.e., unadjusted duration of exposure) = [date of last dose of treatment component – date of first dose of treatment component + 21].

Actual duration of exposure (i.e., adjusted duration of exposure) = min(date of last dose of treatment component + 20, data cut-off date, death date, last contact date for discontinued participants) – (date of first dose of treatment component)+1.

Actual cumulative dose = sum of actual dose (mg) administered for each component at each infusion over all cycles.

Planned cumulative dose = sum of planned dose (mg) administered for each component at each infusion over all cycles, if there were no modifications to dose or schedule.

Actual dose intensity = (actual cumulative dose) / (expected duration of exposure in days/21). Actual dose intensity is calculated per 3-week period, which is why it is divided by 21 in the denominator.

Planned dose intensity = (planned cumulative dose) / (number of cycles)

Relative dose intensity (RDI) is the percentage defined as (Actual Dose Intensity) / (Planned dose intensity) * 100. An RDI of 100% indicates that the drug was administered at the dose planned per protocol, without delay or reductions.

Dose delays, infusion interruptions, missed doses and incomplete infusions will be summarized and listed separately by dose level, treatment component, and treatment arm. These outputs will be produced according to GSK Oncology Data Standards. If study treatment must be delayed for any toxicity, all treatment components must be delayed.

These outputs will also be produced for [redacted] if applicable.

4.5.2. Adverse Events

Analysis of adverse events (AEs), Serious adverse events (SAEs) and Adverse Events of Special Interest (AESI) will be based on GSK Core Data Standards. The details of the planned displays are provided in OPS document.

AEs will be coded using the latest version of MedDRA and grouped by System Organ Class. AEs will be graded by the investigator according to the NCI-CTCAE (version 5.0).

Summaries will focus on treatment emergent adverse events (TEAEs); see Section 6.2.2.3 for the definition. AEs with missing date of onset will be considered to have started on the date of initiation of study treatment and will therefore be classified as TEAEs.

Summary of Adverse Events by System Organ Class, Preferred Term, and Maximum Grade will be reported. Summary of Grade 3-5 AEs, Drug Related Grade 3-5 AEs and Drug Related AEs will be provided by Overall frequency, System Organ Class, Preferred Term, and Maximum Grade.

A summary of number and percentage of participants 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 participant:

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

Summary of non-serious drug related adverse events by overall frequency by PT will be produced.

For disclosure requirements, a summary of common (>=5%) non-serious AEs by SOC and PT (Number of subjects and Occurrences) will be created. The threshold definition 5% should be followed strictly, so a PT occurring 4.99% of subjects should not be included. An event must be reported if it meets the threshold definition of a common non-serious event within **any** treatment group.

Subject level AEs will be available in RAPIDO. Adverse event System Organ Class (SOC), Preferred term (PT) and verbatim text will also be available in RAPIDO.

AEs with missing date of onset will be considered as AEs occurring within the window specified in Section 6.2.2. and will be reported.

AE summaries will be produced for [redacted] if applicable.

4.5.3. Adverse Events of Special Interest

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of adverse event of special interest (AESI). 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 (SRT) agreements in place at the time of reporting.

AESI are comprised of Infusion Related Reactions (IRRs) (PT in the IRR codelist, Relationship to study drug as collected on the AE CRF = Yes and occurred on or within 1 day as a study drug infusion, or on the day after (using the start date of the AE and start date of infusion)) and those of potential immunologic etiology, including irAEs grade ≥ 2 (or AEs of unknown grade). irAEs will be identified by a custom MedDRA query (CMQ) using the following GSK Terms of Interest (TOI) codes:

Table 6 TOI Codes and Categories

TOI Code	TOI category name
322658	Hypersensitivity
322659	Immune-mediated cardiovascular
322660	Immune-mediated endocrinopathies
322661	Immune-mediated Gastrointestinal
322662	Immune-mediated hematologic
322663	Immune-mediated hepatic
322664	Immune-mediated musculoskeletal
322665	Immune-mediated nervous system
322666	Immune-mediated ocular
322667	Immune-mediated Others
322668	Immune-mediated pancreatitis
322669	Immune-mediated Pulmonary
322670	Immune-mediated renal
322671	Immune-mediated skin adverse reactions

IRRs will be identified by a custom MedDRA query (CMQ) using the following GSK Terms of Interest (TOI) code:

TOI Code	TOI category name
323695	Infusion-related reactions

Summaries of the number and percentage of subjects with AESI will be provided for each type of event separately by preferred term and maximum grade. Subject level data on AESI will be available in RAPIDO.

Summary of Onset and Duration of the First Occurrence of AESI will also be produced.

The above outputs will also be produced for CCI [redacted] if applicable.

4.5.4. Additional Safety Assessments

4.5.4.1. Deaths and Serious Adverse Events

All deaths will be summarized and listed to provide participant-specific details on participants who died using primary reason of death.

All SAEs will be tabulated based on the number and percentage of participants who experienced the event. The summary table will be displayed in descending order of total incidence by SOC and PT. Summary of Serious Fatal and Non-Fatal Drug Related AEs will also be provided.

A study treatment-related SAE is defined as an SAE for which the investigator classifies the relationship to any 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.

Subject level SAEs will be available in RAPIDO.

A listing of reasons for considering an SAE will be provided. A listing of non-fatal serious adverse events will also be provided.

SAE's will be reported for CCI [redacted] if applicable.

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

The following subject level data will be available in RAPIDO:

- AEs Leading to Discontinuation of Study Treatment
- AEs Leading to Withdrawal from the Study

An AE leading to dose modification is an AE for which the action with respect to dosing is recorded as interruption of dose. 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.

These outputs will be reported for CCI [redacted] if applicable.

4.5.4.3. Laboratory Data

Laboratory grades will be reported using the Common Terminology Criteria for Adverse Events (CTCAE v5.0). The assessment of laboratory toxicities will examine the following laboratory tests performed by local laboratories:

Table 7 Laboratory assessment parameters

Laboratory Assessments	Parameters			
Hematology	RBC Indices	WBC count with Differential		Platelets
	Hemoglobin	Neutrophils		
	Hematocrit	Lymphocytes		
	RBC count	Monocytes		
		EosinophilsI		
		Basophils		
Clinical Chemistry	BUN[a]	Potassium	Bilirubin	AST (SGOT)
	Creatinine[b]	Sodium	Total protein	ALT (SGPT)
	Glucose	Calcium	Albumin	Alkaline phosphatase
	LDH	Amylase	Lipase	
Coagulation	PT/INR			
	PTT/aPTT			
Cardiac Function	Troponin I High Sensitivity, Troponin I , Troponin T High Sensitivity, Troponin T , BNP, Nt-proBNP			
Thyroid Function	Thyroid stimulating hormone Free T4 Free T3 (when clinically indicated)			
Routine Urinalysis	Specific gravity pH, glucose, protein, blood and ketones by dipstick (Note: routine urinalysis by method other than dipstick is acceptable, in accordance with local practice).			
Other Screening Tests	Hepatitis B surface antigen (HBsAg) Hepatitis C (Hep C antibody)[c] Serum b-hCG Pregnancy test (for women of child bearing potential)			
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; b-hCG = beta-human chorionic gonadotropin; BNP = brain natriuretic peptide; BUN = blood urea nitrogen; HBsAg = Hepatitis B surface antigen; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; T3 = triiodothyronine; T4 = thyroxine; WBC = white				

Laboratory Assessments	Parameters
blood cells; INR = International Normalized Ratio; PT = Prothrombin Time; aPTT = Activated Partial Thromboplastin Time a. Required if local laboratory testing is available b. Creatinine clearance is also required to be calculated using the formula provided in Appendix 9 of the protocol. c. Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained. Hepatitis C RNA Test is optional with negative Hepatitis C antibody test. d. Coagulation factors (PT/INR and aPTT/PTT) should be tested as part of the screening procedures for all participants. Any participant receiving anticoagulant therapy should have coagulation factors monitored closely throughout the study	

Change from baseline by scheduled visits will be summarised using mean, median, standard deviation, minimum, and maximum.

Actual collected values for cardiac function tests will be normalized with respect to the Upper Limit Normal, and the change from baseline will be the difference in the normalized values. Baseline value for the cardiac function tests will be the latest pre-dose assessment with a non-missing normalized value, including those from unscheduled visits.

Summaries of worst-case grade increase from baseline grade will be provided for all the lab tests that are gradable by CTCAE v5.0. These summaries will display the number and percentage of participants 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. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

For lab tests that are not gradable by CTCAE v5.0, summaries of worst-case (including both scheduled and unscheduled) changes from baseline with respect to normal range will be generated via a shift table. The normal range indicator will be determined by comparing actual lab values to the normal range (Low, High, Normal). Missing baseline values will be assumed to have a normal baseline value. In addition, the summary will include worst case changes from baseline with respect to normal range by scheduled visits, including treatment discontinuation and safety follow up.

Separate summary tables for haematology and chemistry laboratory tests will be produced. Coagulation, cardiac function and thyroid function parameters will be reported under chemistry outputs.

Liver function laboratory tests will be included with chemistry lab 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 overall 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).

To be counted in the denominator, the subject must have at least one post-baseline lab chemistry measurement for the specified lab tests (e.g., in the 'ALT ≥3xULN and BIL ≥2xULN' category, the denominator should include subjects who had both a post-baseline ALT value AND a post-baseline BIL value that was up to 28 days after ALT).

An e-DISH plot of maximum post baseline total bilirubin versus maximum post baseline ALT will be created.

Listings for all laboratory data for subjects with any value outside normal range, and for urinalysis data for subjects with any value of potential clinical importance, will be generated. A character lab value starting with '<X' or '>X' will be displayed in listings but will not be imputed with a numeric value thus will not be included for summaries.

4.5.4.4. Vital Signs

The following summaries will be provided for vital signs data by scheduled visits, treatment discontinuation and worst case (including unscheduled visits):

- Summary of Changes in Heart Rate from Baseline
- Summary of Increases in Blood Pressure from Baseline
- Summary of Changes in Temperature from Baseline

A table will be provided summarizing change from baseline for weight, pulse rate, respiratory rate, and oxygen saturation (measured by pulse oximetry) by treatment. This table will include the subject count (n), mean, SD, median, min, and max for each scheduled visit (including post-baseline records and treatment discontinuation).

Subject level data will be available in RAPIDO for the following:

- Vital Signs with Values of Potential Clinical Importance

The oncology standard categories for Heart Rate in bpm is:

- Heart Rate in bpm: 'Decrease to <60', 'Increase to >100'

The oncology standard categories for Systolic Blood Pressure in mmHg are:

- 'Any Grade Increase'
- 'Increase to Grade 2 (140-159)'
- 'Increase to Grade 3 (>=160)'

Note: 'Any Grade Increase' will be footnoted as Grade 0 (<120), Grade 1 (120-139), Grade 2 (140-159), Grade 3 (>=160).

The oncology standard categories for Diastolic Blood Pressure in mmHg are:

- ‘Any Grade Increase’
- ‘Increase to Grade 2 (90-99)’
- ‘Increase to Grade 3 (>=100)’

Note: ‘Any Grade Increase’ will be footnoted as Grade 0 (<80), Grade 1 (80-89), Grade 2 (90-99), Grade 3 (>=100).

The oncology standard category ‘Decrease to < 90’ will be used for the Summary of decreases in Systolic Blood Pressure from Baseline.

The oncology standard categories for Temperature are:

- <=35° C = Low
- >= 38° C = High
- 35° C – 38° C = Normal

Subjects with a missing baseline value are assumed to have a normal baseline value. Missing baseline grade will be assumed to be Grade 0.

4.5.4.5. Performance Status

ECOG performance status will be summarized at baseline and each post-baseline scheduled visit. Summaries will use frequency and percentage of participants at each planned assessment time.

4.5.4.6. ECG

A summary of the number and percentage of participants who had normal and abnormal (clinically significant and not clinically significant) ECG findings will be displayed by scheduled visits (including treatment discontinuation) as well as for the worst-case post-baseline (where worst-case includes all collected scheduled and unscheduled visits).

The QTcF values based on Fridericia formula will be rounded to the integer and the values will be categorized into the following ranges, inclusively: Grade 0 (<450 msec), Grade 1 (≥450-≤480 msec), Grade 2 (≥481-≤500), and Grade 3 (≥501). Summaries of grade increase will be provided. These summaries will display the number and proportion of participants with any grade increase, increase to grade 2 and increase to grade 3 at each scheduled assessment time and in the worst-case post-baseline. Missing baseline grades will be assumed to be Grade 0.

The changes in QTcF values will be categorized into the clinical concern ranges in QTc: increase of ≤30 msec, 31-60 and >60 msec. A summary of change in QTcF value will display the number and proportion of participants with a change within each range at each scheduled assessment time and in the worst-case post-baseline. Participants with missing baseline values will be excluded from this summary.

Subject level data of ECG data, such as abnormal ECG findings and ECG values, will be available in RAPIDO.

4.5.4.7. LVEF

LVEF change from baseline will be summarized by scheduled visits (including treatment discontinuation) as well as for the worst-case post-baseline (where worst-case includes all collected scheduled and unscheduled visits). Summary tables will contain count and percentage of participants with >0-<10 Decrease, 10-19 Decrease, >=20 Decrease, >=10 Decrease and >= LLN, >=10 Decrease and < LLN, >=20 Decrease and >= LLN and >=20 Decrease and < LLN in LVEF from baseline. LVEF subject level data will be available in RAPIDO.

4.6. Other Analyses

CCI

4.7. Changes to Protocol Defined Analyses

Below are the changes or deviations to the originally planned statistical analysis specified in the protocol amendment 10 (Dated: [26-April-2023]).

Table 8 Changes to Protocol Defined Analysis Plan

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
• Section 10.4: PK analysis will consist of the ITT population	• PK analysis will consist of all patients from the safety population.	• ITT is only defined for Arm 5 randomized PK/PD cohort. PK analysis should include all cohorts.

5. SAMPLE SIZE DETERMINATION

The safety dose escalation cohort and expansion PK/PD cohort in Arm 4 will enroll a maximum of 24 participants across all dose combinations.

The safety dose escalation cohort in Arm 5 will enroll a maximum of 9 DLT evaluable participants for DLT evaluation for each dose combination.

The randomized PK/PD expansion cohort in Arm 5 will enroll a maximum of 30 participants across the dose levels.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

The study population analyses will be based on the safety analysis set for Arm 4 and Arm 5 - Safety, and on the ITT set for Arm 5 – Randomized, unless otherwise specified.

Study population analyses including analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, past and current medical conditions, prior and concomitant medications, disease characteristics at initial diagnosis and at screening, prior, on treatment and follow-up anti-cancer therapy, surgical/medical procedures, substance use, duration of follow up, will be based on GSK Core and Oncology Data Standards. Details of the planned displays are presented in OPS document.

6.1.1. Participant Disposition

A summary of the number of subjects in each of the analysis populations described in Section 3 will be provided using the Screened population.

A summary of subject status and reason for study withdrawal will be provided. This display will show the number and percentage of subjects who have completed the study or have withdrawn 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 (Electronic Case Report Form). Subjects who die for any reason during on study treatment period or follow up period will be considered to have completed the study.

A summary of study treatment status will be provided. This display will show the number and proportion of subjects who 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 treatment discontinuation will be generated. The listing will include last dose date and primary reasons for study treatment discontinuation. A listing of reasons for study withdrawal will also be generated.

A listing of screen failures will be generated, as well as a screening status summary table.

Summary table of subject status and treatment status will be produced for CCI [redacted] if applicable. Corresponding dynamic listing will be available in RAPIDO.

The number of subjects will be summarized by Country, Site ID, and Investigator ID. This summary must be produced based on the enrolled population for Arm 4 and Arm 5 Safety, and for the ITT population for Arm 5 Randomized. The total column, summarizing subjects regardless of treatment, should always be included. Rows should be sorted alphabetically by country, then in numerical order by Site ID. As needed, summaries and listings required by the FDA Administration Amendments (FDAAA) and EU Clinical Trials Regulation (CTR) will be provided.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics (e.g., age, race, ethnicity, sex and height) will be listed and summarized. Age and height will be summarized using the mean, standard deviation, minimum, median, and maximum. Age will also be categorized as 18-64, 65-74, 75-84, and ≥85 in demographic tables, and as 18-64, 65-84, and ≥85 in the summary of age ranges table. The count and percentage will be computed for age categories, race, ethnicity, and sex.

The demographic summary will also be produced for CCI [redacted] if applicable.

Past medical conditions and current medical conditions as of screening will be summarized respectively.

Substance use, including smoking history, tobacco use, alcohol history will be summarized.

6.1.3. Protocol Deviations

Important protocol deviations will be summarized 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. These protocol deviations will be reviewed to identify those considered as important as follows:

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

A separate 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.

6.1.4. Prior and Concomitant Medications

Prior medications will be coded using WHO Drug coding dictionary and summarized. The summary of prior medications will show the number and percentage of subjects taking prior medications by Ingredient.

Concomitant medications will be coded using WHO Drug coding dictionary and summarized. 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.

In the summary of concomitant medications, each subject is counted once within each unique ingredient. For example, if a subject takes Amoxicillin 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.

Note: In order to be considered a concomitant medication, the concomitant medication must have been taken at some point on-treatment. Please refer to Section 6.2.2 for the definition of on treatment period.

These outputs will also be produced for CCI [redacted] if applicable.

6.1.5. Prior Medical Condition and Disease Characteristics

Disease history and baseline disease characteristics (primary tumour type, lesion status, time since initial diagnosis, stage at initial diagnosis, time since last disease progression, sites of metastatic disease at screening) will be summarized. Details of the derivations are specified in the OPS. Indicators (yes/no) for the following, collected at screening, will also be summarized: measurable disease, non-target lesions, and metastatic disease. Medical conditions present at screening will be listed and will be summarized by past and current. Disease history and characteristics, number of prior chemotherapies, as well as these medical conditions, will be available as dynamic listings in RAPIDO.

A summary of disease burden at baseline will be provided.

Prior surgeries will be available in RAPIDO.

These outputs will also be produced for CCI [redacted] if applicable.

6.1.6. Prior and Subsequent Anti-cancer Therapy

Anti-cancer therapy will be coded using the latest version of the WHO Drug dictionary. Prior anti-cancer therapy will be coded using WHO Drug coding dictionary, then summarized by type of therapy and available in RAPIDO. Therapies will be classified by type (chemotherapy, immunotherapy, hormonal therapy, biologic therapy, radioactive therapy, small molecule targeted therapy, and radiotherapy) . A listing of prior anti-cancer therapy will show the relationship between Anatomical Therapeutic Chemical (ATC) Level 1, ingredient, and verbatim text;

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

The prior and follow-up anti-cancer therapies will be summarised by ingredient. The number and percentage of subjects that received different types of follow-up anti-cancer therapies will include the time from study treatment discontinuation to start of follow-up therapy (days). Subject level Prior and Follow-up anti-cancer therapy information will be provided in RAPIDO. A summary table and a listing for on-treatment radio therapies will be produced. Please refer to Section 6.2.2 for the definition of on treatment period.

These outputs will also be produced for [redacted] if applicable.

6.1.7. Additional Analyses Due to the COVID-19 Pandemic

Confirmed, probable and suspected COVID 19 cases will be summarized and subject level data can be found RAPIDO. Visits impacted by COVID-19 Pandemic will be summarized. Number of subjects with missed visits, site visits with one or more assessment missed, remote visit with no assessments missed and remote visit with one or more assessments missed will be summarized with primary reason for the impact.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Criteria for Potential Clinical Importance

Reference ranges for all laboratory parameters collected throughout the study are provided by each site. 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. For laboratory data, out of range will be considered as Potential Clinical Importance. A static listing of all laboratory data for subjects with any value outside normal range will be generated.

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0) will be used to assign grades to the relevant laboratory parameters, blood pressure and QTc.

6.2.2. Study Period

Adverse events, ECOG, physical examination, clinical chemistry, haematology, urinalysis, and other safety domains will be assigned to the study phases defined below. Partial dates will be imputed into full dates, if applicable, for slotting data to the appropriate categories below.

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

Table 9 Study Phase Definitions

Study Phase	Definition
Pre-Treatment	Date < Study Treatment Start Date

Study Phase	Definition
On-Treatment	Study Treatment Start Date ≤ Date ≤ Study Treatment Stop Date + 30 days
Post-Treatment	Date > Study Treatment Stop Date + 30 days

For parameters where time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

6.2.2.1. Study Phases for Concomitant Medications

Table 10 Study Phases for Concomitant Medications

Study Phase	Definition
Prior	Prior medications are medications, other than study treatment, that started and stopped prior to the first dose of study treatment.
Concomitant	Any medication that is not a prior. Concomitant medications are medications, other than study treatment, that are not prior medications, with a start date prior to, on, or after the start of the first dose of study treatment and before a study treatment discontinuation date plus 30 days. The stop date must be on or after the start of the first dose of study treatment. If the stop date is missing, it is considered concomitant. Derivations of prior/concomitant medications will use imputed dates where possible/necessary. If the medication start date is prior to the treatment start date and the stop date is missing, the medication will be classified as concomitant. If both start and stop dates are missing, then it is concomitant.
Follow-Up	Medications other than study treatment with a start date after treatment discontinuation plus 30 days.

NOTES:
Please refer to Section 6.2.6 for Handling of Partial and Completely missing dates for concomitant medication. Derivations of prior/concomitant medications will use imputed dates were possible and necessary.

6.2.2.2. Study Phases for Anti-cancer Therapy

Table 11 Study Phases for Anti-cancer Therapy

Study Phase	Definition
Prior	Anti-cancer therapy Date < Study Treatment Start Date

Study Phase	Definition
On-treatment	Study Treatment Start Date ≤ Anti-cancer therapy Date ≤ Study Treatment Stop Date
Follow-up	Anti-cancer therapy Date > Study Treatment Stop Date

6.2.2.3. Treatment Emergent Flags for Adverse Events

Table 12 Treatment Emergent Flags for Adverse Events

Flag	Definition

Treatment Emergent	For AEs:
	• Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 30 days
	
	For SAEs/AESIs:
	• If Date of Follow Up Anti-Cancer Therapy ≤ Study Treatment Stop Date + 30 days:
	  • Study Treatment Start Date ≤ AE Start Date or pre-existing (prior to exposure) AE Worsening Date ≤ Study Treatment Stop Date + 30 days.
	• Otherwise:
	  • Study Treatment Start Date ≤ AE Start Date or pre-existing (prior to exposure) AE Worsening Date ≤ Study Treatment Stop Date + 90 days or Date of Initiation of Follow Up Anti-Cancer Therapy, whichever comes first.

NOTES:
- If AE start date is missing, then the AE will be considered to be treatment emergent.
- If the study treatment stop date is missing, then the AE will be considered to be treatment emergent.
- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

6.2.3. Study Day and Reference Dates

The safety reference date is the study intervention start date and will be used to calculate study day for safety measures.

The study day is calculated as below:

- Ref Date = Missing → Study Day = Missing
- Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
- Ref Date ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

6.2.4. Assessment Window

The visit assigned to the assessment as entered in the CRF (nominal visit) will be used for reporting.

6.2.5. Multiple Measurements at One Analysis Time Point

If there are two values for the same visit or if an unscheduled visit occurred on the same date and time, the values will be averaged for all summary calculations. For relevant listings, all data will be presented.

Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.

6.2.6. Handling of Partial Dates

Table 13 Handling of Partial Dates

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>• Partial dates will be displayed as captured in participant listing displays.
• However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study phases or for specific analysis purposes as outlined below.
• Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.</td></tr>
<tr><td>Adverse Events</td><td>• Partial dates for AE recorded in the CRF will be imputed using the following conventions:
<table><tr><td>Missing start day</td><td>If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = 1st of month.

Else if study intervention start date is not missing:</td></tr></table></td></tr>
</table>

Element	Reporting Detail	
		• If month and year of start date = month and year of study intervention start date, then – If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month. – Else set start date = study intervention start date. Else set start date = 1st of month.
	Missing start day and month	If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = January 1. Else if study intervention start date is not missing: • If year of start date = year of study intervention start date, then – If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1. – Else set start date = study intervention start date. Else set start date = January 1.
	Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year).
	Missing end day and month	No Imputation
	Completely missing start/end date	No imputation
Concomitant Medications/Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:	
	Missing start day	If study intervention start date is missing (i.e., participant did not start study

Element	Reporting Detail	
		intervention), then set start date = 1st of month. Else if study intervention start date is not missing: • If month and year of start date = month and year of study intervention start date, then – If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month. – Else set start date = study intervention start date. Else set start date = 1st of month.
	Missing start day and month	If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = January 1. Else if study intervention start date is not missing: • If year of start date = year of study intervention start date, then – If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1. – Else set start date = study. intervention start date. Else set start date = January 1.
	Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year).
	Missing end day and month	A '31' will be used for the day and 'Dec' will be used for the month.
	Completely missing start/end date	No imputation

Element	Reporting Detail

Follow-up Anti-Cancer Therapy/ Radiotherapy/ Surgical Procedures for Efficacy Evaluation (e.g., response rate, time to event)	• Completely missing start dates will remain missing, with no imputation applied.
	• Partial start dates will be imputed using the following convention:
	  • If both month and day are missing, no imputation will be applied.
	  • If only day is missing:
	  o If the month of partial date is the same as the month of last dosing date, minimum of (last dosing date + 1, last day of the month) will be used for the day.
	  o If the month of partial date is the same as the month of last disease assessment and the last disease assessment is PD as per RECIST 1.1, minimum of (last date of disease assessment + 1, last day of the month) will be used for the day.
	  o If both conditions above are met, the later date will be used for the day.
	  o Otherwise, a '01' will be used for the day.
	Completely or partial missing end dates will remain missing, with no imputation applied;

6.2.7. Early PK Access Key Activities

Not applicable. The study is open label with no blinding element.

6.2.8. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
WinNonlin

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