Statistical Analysis Plan

Study ID: 205801-002 (Sub-study 2)

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: NCT06790303

Date of Document: 14-Oct-2021

Note: Platform trial 205801 comprises several arms, each individually registered on ClinicalTrials.Gov. This SAP document pertains specifically to Arm 3 of Sub-study 2. 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 2 was not available when this SAP was being developed.

Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol 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 The purpose of this SAP is to describe the planned final analyses and outputs for Arm 3 in the Clinical Study Report (CSR) for 205801.
Study Number:	205801
Compound Number:	GSK3359609
Abbreviated Title:	Phase II NSCLC Master Protocol
Acronym:	ENTRÉE Lung

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number

Registry	**ID**
Clinicaltrials.gov	NCT03739710

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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
RAP V3	08 Mar 2021	04	Not Applicable	Original version
SAP amendment 1	Refer Document Date	05	1. Analysis and reporting of part 2 have been omitted. 2. List of TLF's are reduced just to support closure activities. 3. The term "Sub-study" is changed to "Arm" 4. Owing to the study termination the study team has collectively decided not to analyse data for the following endpoints: PK	The study is getting terminated in part 1.

1. INTRODUCTION

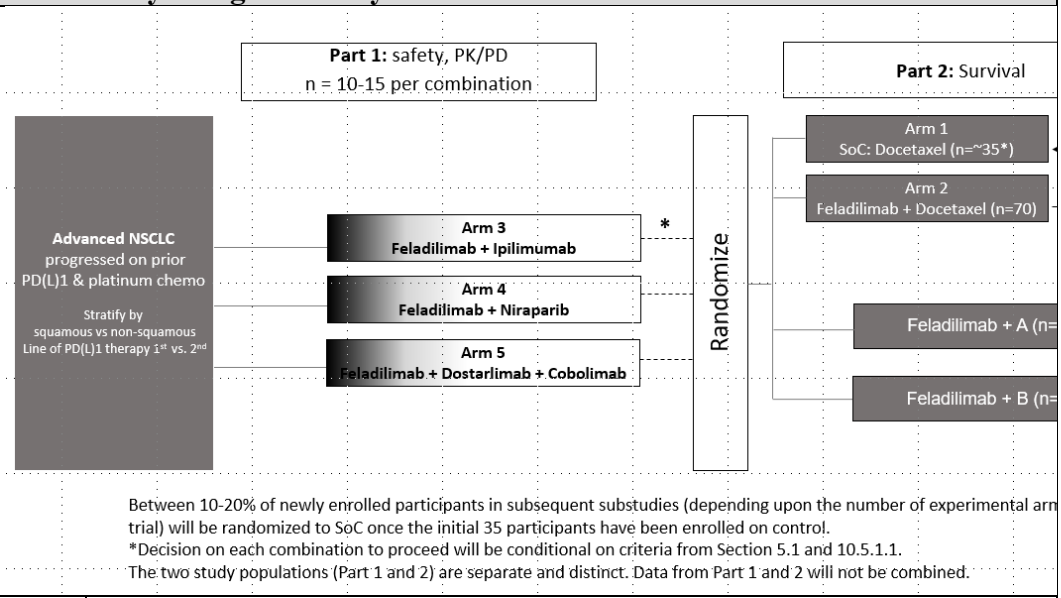
The purpose of this SAP is to describe the planned final analyses and outputs for arm 3 in the Clinical Study Report (CSR) for 205801.

1.1. Objectives, Estimands and Endpoints

Part 1:

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

1.2. Study Design

Overview of Study Design and Key Features	
	
Design Features	• A randomized, open-label, platform trial utilizing a master protocol • The study has 2 parts, i.e. part 1 and part 2. • Part 1 is a non-randomized part based on safety and pharmacokinetics/pharmacodynamics (PK/PD) evaluation. Part 2 is a randomized part, comparing the efficacy and safety of these novel regimens with SoC. • If the study passes part 1, then the participants will be recruited for part 2. • The final analysis for part 1 will be performed once all the participants complete 2 post baseline tumour assessments. • For part 2, interim analysis will be performed once 45 death events (18 in combination arm) are observed in the study. The primary analysis will be performed when 75 events are observed, and final analysis will be performed when 85 events are observed. • Arm 3 is getting terminated in part 1.
Study intervention	• The study will evaluate the safety and efficacy of feladilimab (ICOS agonist) in combination with ipilimumab. • There is no dose escalation in part 1, but the safety will be evaluated based on mTPI process • Combination study treatment will continue to be administered at the indicated schedule for a maximum duration of approximately 2 years or up to 35 treatment visits whichever comes first, or until disease progression as determined by iRECIST, death, unacceptable toxicity, or other protocol-defined criteria are met.

<table>
<tr><th colspan="6">Overview of Study Design and Key Features</th></tr>
<tr><td></td><td></td><td>Treatment Arm</td><td>Dosage</td><td>Route of Administration</td><td>Dosing Frequency</td></tr>
<tr><td></td><td></td><td>Feladilimab</td><td>24 mg</td><td>IV infusion</td><td>Once Q3W</td></tr>
<tr><td></td><td></td><td>Ipilimumab</td><td>1 mg/kg or 3 mg/kg</td><td>IV infusion</td><td>Once Q3W</td></tr>
<tr><td>Study intervention Assignment</td><td colspan="5">• In part 1, participants will be assigned to either 1mg/kg or 3mg/kg ipilimumab cohort depending on study team’s decision.</td></tr>
<tr><td>Interim Analysis</td><td colspan="5">• No interim analysis will be performed in part 1.</td></tr>
</table>

2. STATISTICAL HYPOTHESES

Part 1: 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

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility.	• Study Population
Safety	• All randomized participants who received at least one dose of SoC or experimental regimen based on actual treatment received.	• Safety
Intent-To-Treat (ITT)	• All participants who were randomized to treatment regardless of whether the participants actually received study treatment.	• Study Population • Efficacy
DLT Evaluable	• A subset of participants in part 1 who have received the first course of treatment containing both agents within an arm and followed up for a 21-day period or withdrawn within 21 days due to an AE meeting the definition of a DLT. • For oral dosing, a participant is considered DLT evaluable if they received at least 80% the first course of treatment containing both agents within an arm	• DLT

Population	Definition / Criteria	Analyses Evaluated
	and followed up for a 21-day period or withdrawn within 21 days due to an AE meeting the definition of a DLT	

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Safety analysis set will be used for all study population analyses, safety analyses, and efficacy analyses.

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.

4.1.2. Baseline Definition

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. For laboratory data, baseline will be the latest non-missing pre-dose value from local lab will be used.

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 endpoint is DLT rate, AE's and SAE's. The analysis and reporting of AE's and SAE's are discussed in Section 4.5.

4.2.1. Definition of DLT

A DLT is defined as an AE that meets at least one of the criteria listed in protocol and is considered by the investigator to be clinically relevant and attributed (probably or possibly) to the study treatment during the 21-day DLT observation period.

4.2.2. Main analytical approach

A listing of adverse events recorded as dose-limiting toxicities during the determinative period will be provided. Additionally, a summary of the number of patients experiencing DLTs will also be provided.

4.2.3. Sensitivity analyses

No sensitivity analysis will be performed.

4.2.4. Additional estimands

No additional estimands are defined.

4.3. Secondary Endpoint(s) Analyses

4.3.1. Secondary endpoints

The secondary endpoints in part 1 are, Overall Response Rate (ORR) and Disease Control Rate (DCR).

4.3.1.1. Definition of Overall Response Rate (ORR) and Disease Control Rate (DCR)

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 best overall confirmed complete response, partial response or stable disease at any time as per RECIST1.1

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 8 weeks (56 days) from baseline. If the minimum of 8 weeks (56 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 8-week requirement the best response will be PD. Alternatively, subjects lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

If NE (Not Evaluable) is recorded in between initial and confirmatory CR or PR then it can disregarded to obtain the Best Response

A SD in between an initial PR and confirmation PR can also be disregarded to obtain the Best Response of PR (see below table)

4.3.1.2. Main analytical approach

ORR

The number and percentage of participants with the BOR in the following response categories will be summarized: CR, PR, iCR, iPR. The corresponding exact 95% CI for ORR and iORR 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 subject level responses will be generated.

DCR

The number and percentage of participants with the BOR in the following response categories will be summarized: CR, PR, SD, iCR, iPR, iSD. The corresponding exact 95% CI for DCR and iDCR 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.

4.3.2. Supportive secondary endpoint(s)

No other secondary endpoints are defined.

4.4. Exploratory Endpoint Analyses

CCI [redacted]

4.5. Safety Analyses

The safety analyses will be based on the Safety population.

4.5.1. Extent of Exposure

Extent of exposure to experimental arm will be summarized by Number of cycles, relative dose intensity and duration of exposure.

Relative dose intensity (RDI) is the percentage of the actual dose delivered relative to the intended dose. Relative dose intensity (RDI) is defined as (Actual cumulative dose

delivered up to treatment discontinuation)/(Planned cumulative dose up to treatment discontinuation)*100. The planned cumulative dose is the total dose that would be delivered, if there were no modification to dose or schedule. An RDI of 100% indicates that the drug was administered at the dose planned per protocol, without delay or reductions.

Treatment compliance is defined as (Actual cumulative dose/Scheduled cumulative dose)*100. The scheduled dose accounts for any dose reductions, for example, if a participant had a dose reduction from 75 mg/m^2 to 60 mg/m^2, then the scheduled dose is 60 mg/m^2.
Summary statistics will be produced for extent of exposure.

Duration of Exposure in weeks is defined as (treatment stop date – treatment start date + 1) divided by 7.

Dose reductions, infusion interruptions and incomplete infusions, and dose delays will be listed separately by dose.

4.5.2. Adverse Events

Adverse events analyses including the analysis of adverse events (AEs), Serious adverse events (SAEs) and other significant AEs will be based on GSK Core Data Standards. Dose modifications, dose interruptions, dose reduction, and dose delays will be listed according to GSK Oncology Data Standards. The details of the planned displays are provided in OPS document.

AEs will be coded using the standard MedDRA v.21.1. and grouped by system organ class. AEs will be graded by the investigator according to the NCI-CTCAE (version 5.0).

Summary of all Adverse Events and Drug related Adverse events by System Organ Class and Preferred Term and Maximum Grade will be reported. Summary of Grade 3-5 AEs and drug related Grade 3-5 AEs that occurred in ≥5% of participants will be provided by Overall frequency.

A summary of non-serious AEs that occurred in strictly 5% of the participants 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).

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.

All AEs will be listed. Additionally, a listing of subject IDs for each individual AE will be produced. Listing of relationship of adverse event System Organ Class (SOC), Preferred term (PT) and verbatim text will be produced.

AEs with missing date of onset will be considered treatment emergent.

4.5.2.1. Adverse Events of Special Interest

No AESI are reported in part 1.

4.5.2.2. COVID-19 Assessment and COVID-19 AEs

Confirmed, probable and suspected COVID 19 cases will be summarized and listed. 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.

4.5.3. Additional Safety Assessments

4.5.3.1. Deaths and Serious Adverse Events

All deaths will be listed to provide participant-specific details on participants who died.

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 Drug related SAE, fatal SAE, drug-related fatal SAE will also be produced

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.

A listing of reasons for considering an SAE will be provided.

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

Following listings will be provided,

- 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 reduction or 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.

4.5.3.3. Pregnancies

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. If subjects become pregnant while on the study, the information will be included in the narratives and no separate table or listing will be produced.

4.5.3.4. 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:

Laboratory Assessments	Parameters			
Hematology	RBC Indices	WBC count with Differential		Platelets
	Hemoglobin	Neutrophils		
	Hematocrit	Lymphocytes		
	RBC count	Monocytes		
		Eosinophils		
		Basophils		
Clinical Chemistry	BUN[a]	Potassium	Bilirubin	AST (SGOT)
	Creatinine[b]	Sodium	Total protein	ALT (SGPT)
	Glucose	Calcium	Albumin	Alkaline phosphatase
	LDH			
Coagulation	INR or PT			
	PTT/aPTT			
Cardiac Function	Troponin I or Troponin T			
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 β-hCG Pregnancy test (for women of child bearing potential)			

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; 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 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.

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. 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 labelled bi-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 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 participant has a "Decrease to low" and an "Increase to high" during the same time interval, then the participant is counted in both the "Decrease to Low" category and the "Increase to High" category. 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.

Listing of Laboratory values of Potential Clinical Importance and listing of all laboratory values for any value of potential clinical importance will be produced

A separate listing of laboratory data with character values will also be provided. Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of participants with non-missing value at each visit.

Urinalysis Results will be summarised. Worst-case Urinalysis Results Post-Baseline Relative to Baseline will be summarised

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.

4.5.3.5. Vital Signs

The following summaries will be provided for vital signs data:

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

- Summary of Changes in Temperature from Baseline

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 of clinical concern for Temperature are:

4.6. Other Analyses

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.

4.6.1. Subgroup analyses

No subgroup analysis is planned in this study.

4.7. Interim Analyses

No interim analysis is planned in part 1.

4.8. Changes to Protocol Defined Analyses

Changes from the originally planned statistical analysis specified in the protocol are detailed in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
• Analysis and reporting of part 2 of the study	• No part 2 analysis is described	• The study is getting terminated in part 1

5. SAMPLE SIZE DETERMINATION

Part 1:

A maximum of 15 participants will be enrolled to each scheduled dose level of ipilimumab in Part 1.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

The study population analyses will be based on the Safety, unless otherwise specified.

Study population analyses including analyses of subject'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, will be based on GSK Core and Oncology Data Standards.

6.1.1. Participant Disposition

A summary of the number of subjects in each of the analysis sets described in Section 3 will be provided. Number of subjects based on the Safety will be summarized by country and site for each dose level.

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 and secondary (if any) 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-treatment 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 percentage 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.

The number of subjects will be summarized by Country, Site ID and Investigator ID. This summary must be produced based on the safety population. 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

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics (e.g., age, race, ethnicity, sex, height, and baseline body weight) will be listed and summarized. Age, height and weight will be summarized using the mean, standard deviation, minimum, median, and maximum. In addition, age will also be categorized and summarized by 18-64, 65-74, 75-84, and ≥85. The count and percentage will be computed for race, ethnicity and sex.

A separate summary of age ranges based on the ITT population will be provided. Age will be summarized in categories: 18-64, 65-84, and ≥85. Race and racial combinations will also be summarized. Listing of Race will also be provided.

6.1.3. Protocol Deviations

Important and non-important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and important protocol deviations will be listed. Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.

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

A separate 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 GSK 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 GSK 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, using CMBASECD and CMBASE.

Concomitant medications will be summarized separately for medications with onset date within the on-therapy period and for medications with onset date within the pre-therapy period. Note: In order to be considered a concomitant medication, the concomitant medication must have been taken at some point during the on-therapy window.

6.1.5. Prior Medical Condition and Disease Characteristics

Disease history and characteristics (primary tumor type, lesion status, time since initial diagnosis, stage at initial diagnosis, time since last progression) will be summarized. 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, as well as these medical conditions, will be presented in data listings.

A summary of disease burden at baseline will be provided. Information on sites of metastatic disease at screening will be summarized.

Prior cancer related surgeries will be summarized and listed.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Criteria for Potential Clinical Importance

To identify values of potential clinical importance, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v [5.0]) will be used to assign grades for laboratory parameters including clinical chemistry, hematology, liver function tests, QTc (Fridericia's) values, LVEF and vital signs (heart rate, blood pressure, temperature).

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.

6.2.2. Study Period

6.2.2.1. Study Phases

Adverse events, serious adverse events, death 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. Flag variables (time in relation to study phase) indicating the study time periods will be added to the ADaM variable APHASE, and the treatment emergent AE flag will be created to ADAE variable TRTEMFL.

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

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

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

6.2.2.2. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before 28 days prior to study treatment start date
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Section 6.2.6.: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

6.2.2.3. Treatment Emergent Flag for Adverse Events

Flag	Definition

Treatment Emergent	**Non-serious AEs**
	In general, all AEs with a start date after treatment are considered emergent regardless of AE start date is before or after treatment stop date.
	• If AE onset date is on or after treatment start date & on or before treatment stop date + 30 days
	  ○ Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 30 days
	  ○ AE Start Date is missing
	Serious AE/AESI
	  ○ If AE onset date is on or after treatment start date & on or before treatment stop date + 30 days Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 30 days
	  ○ AE Start Date is missing
	Missing AE Start Date will be imputed following rules in Section 12.7.2.1 for determining Treatment Emergent AEs.

NOTES:

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

6.2.3. Study Day and Reference Dates

Study Day for Safety

• Calculated as the number of days from First Dose Date:
  ○ 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

Study Day for ITT

• Calculated as the number of days from Randomization Date:
  ○ Ref Date = Missing → Study Day = Missing
  ○ Ref Date < Randomization Date → Study Day = Ref Date – Randomization Date
  ○ Ref Date ≥Randomization Date → Study Day = Ref Date – Randomization 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

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.

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>
<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.
• 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>• Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings.
• 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 treatment start date is missing (i.e. participant did not start study treatment), then set start date = 1st of month.
• Else if study treatment start date is not missing:
o 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.</td></tr></table></td></tr>
</table>

Element	Reporting Detail	
		▪ Else set start date = study treatment start date. o Else set start date = 1st of month.
	Missing start day and month	• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = January 1. • Else if study treatment start date is not missing: o 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. o Else set start date = January 1.
	Missing stop day	Last day of the month will be used.
	Missing stop day and month	No Imputation
	Completely missing start/end date	No imputation
Concomitant Medications/ Blood Supportive Products	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:	
	Missing start day	• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = 1st of month. • Else if study treatment start date is not missing: o 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. o Else set start date = 1st of month.
	Missing start day and month	• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = January 1. • Else if study treatment start date is not missing:

Element	Reporting Detail	
		○ 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.
	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
New 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: ○ If the month of partial date is the same as the month of last dosing date, minimum of (last dosing date + 1, last day of the month) will be used for the day; ○ If the month of partial date is the same as the month of last disease assessment and the last disease assessment is PD, minimum of (last date of disease assessment + 1, last day of the month) will be used for the day; ○ If both conditions above are met, the later date will be used for the day; ○ Otherwise, a '01' will be used for the day; • Completely or partial missing end dates will remain missing, with no imputation applied;	
ECG	• Missing baseline values are assumed to have baseline value <450 for QTc	

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