STATISTICAL ANALYSIS PLAN

204686

Statistical Analysis Plan for A Phase I, Open-Label Study of GSK1795091 Administered in Combination with Immunotherapies in Participants with Advanced Solid Tumors

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, safety, pharmacokinetic (PK) and pharmacodynamic data for Protocol 204686. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol amendment 6, dated 08th September 2020.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. PRIMARY OBJECTIVE AND ENDPOINTS

The primary objective and endpoint is the following:

Objectives	Endpoints
To evaluate the safety and tolerability of GSK1795091 when administered in combination with GSK3174998, GSK3359609, or Pembrolizumab.	Adverse Events (AEs), Serious Adverse Events (SAEs), Dose Limiting Toxicities (DLTs), withdrawals due to AEs, dose reductions or delays, and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters).

2.2. SECONDARY OBJECTIVES AND ENDPOINTS

The secondary objectives and endpoints are the following:

Objectives	Endpoints
To evaluate the antitumor activity of GSK1795091 when administered in	Objective response rate (ORR) and disease control rate (DCR) (complete response [CR]+

combination with GSK3174998, GSK3359609, or Pembrolizumab	partial response [PR] + stable disease [SD] ≥12 weeks), time to response, duration of response, progression-free survival (PFS), and overall survival (OS).
To characterize the pharmacokinetics (PK) of GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or Pembrolizumab.	GSK1795091 concentrations in plasma and assessment of PK parameters (e.g., Cmax, AUC(0-τ) and Ctrough) if data permit.
To evaluate the immunogenicity of GSK3174998, GSK3359609, and Pembrolizumab when administered in combination with GSK1795091.	Number and percentage of participants who develop detectable Anti-Drug Antibodies (ADA) against GSK3174998, GSK3359609, or Pembrolizumab.

2.3. EXPLORATORY OBJECTIVES AND ENDPOINTS

The exploratory objectives and endpoints are the following:

Objectives	**Endpoints**
To evaluate the immunologic effects of GSK1795091 when administered in combination with GSK3174998, GSK3359609, or Pembrolizumab.	Assessments of OX40 or ICOS receptor expression and occupancy of GSK3174998 or GSK3359609 on immune cells in the peripheral blood. Assessment of the phenotype, quantity, and activation state of T cells and other immune cells in peripheral blood. Assessment of tumor biopsies by immunohistochemistry or related technologies which may include but is not limited to the numbers of tumor-infiltrating lymphocytes

	and other cells expressing key phenotypic markers.
To explore the association between treatment with GSK1795091 when administered in combination with GSK3174998, GSK3359609, or Pembrolizumab and measures of gene expression and immune function.	Assessment of gene expression and immune function from study participants tumor tissue and/or blood samples may include but is not limited to immune related gene expression (RNA expression or RNAseq), gene signatures, and T-cell receptor DNA sequences. Assessment of soluble factors from study participants blood samples and/or tumor may include but is not limited to cytokines and stress-related proteins, cell free DNA (cfDNA), and exosomes.
To explore the association between treatment with GSK1795091 when administered in combination with GSK3174998, GSK3359609, or Pembrolizumab and biomarkers which may be associated with response. To explore the utility of these measures to enrich for clinical efficacy and/or development of a diagnostic test.	Comparison between antitumor activity and baseline biomarker samples from study participants blood and/or tumor which may include but are not limited to DNA, gene expression (RNA), proteins, immune cell phenotypes, and immune response markers. Analysis of the data to identify potential selection biomarkers for participant enrichment.
To characterize the PK of GSK3174998, GSK3359609, or Pembrolizumab when administered in combination with GSK1795091.	GSK3174998, GSK3359609, or Pembrolizumab concentrations in plasma/serum and assessment of PK parameters (e.g., maximum observed concentration [Cmax], AUC(0-τ) and trough concentration [Ctrough]) if data permit.

To explore PK-Pharmacodynamic relationships, such as between PK parameters and antitumor activity, safety or pharmacodynamic markers after treatment with GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or Pembrolizumab.	Evaluation of the relationship of antitumor activity as assessed by ORR, DCR, safety and/or pharmacodynamic markers with PK parameters (e.g., Cmax).
Pharmacogenetics (PGx): To evaluate the association of genetic variations in the host DNA and response to therapy.	Germline genetic evaluations may be conducted to test for association with: - Response to treatment, including GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or Pembrolizumab. Disease susceptibility, severity, and progression and related conditions.
To explore the gut microbiome composition and relationship to treatment response.	Sequencing of the microbiome from stool samples. Analysis of the data to identify potential selection biomarkers for participant enrichment Evaluation of the relationship between antibiotic/probiotic use prior to treatment and antitumor activity
To evaluate disease and treatment related symptoms and impact on function and health-related quality-of-life.	Qualitative telephone interview.

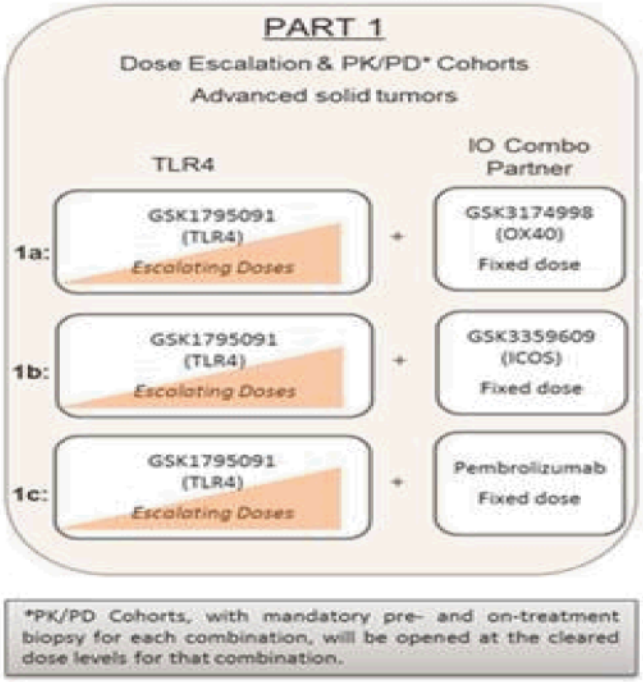
3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a Phase I, open-label, non-randomized, multicenter, multi-country study designed to evaluate the safety, tolerability, PK, pharmacodynamic, and preliminary clinical activity of GSK1795091 administered in combination with other immunotherapies to participants with advanced solid tumors.

This study consists of 2 parts; Part 1 is the dose escalation phase and Part 2 is the dose expansion phase. Following protocol amendment 6, further enrolment was stopped and Part 2 of the study was not open as the development of GSK1795091 was discontinued by GSK.

3.1.1. FIGURE 1: STUDY DESIGN



3.2. STUDY DESIGN FOR THE DOSE ESCALATION PHASE

Part 1 is designed to evaluate the safety and tolerability of escalating doses of GSK1795091 with a single dose level of combination partners in participants with advanced cancers according to a Neuenschwander-Continual Reassessment Method (N-CRM) design [Neuenschwander, 2008] to identify a dose for evaluation in Part 2. Starting at 50 ng, up to 5 different dose levels of GSK1795091 are planned to be evaluated for Part 1. Dose levels of the combination partners will remain fixed.

GSK1795091 combination partners are:

- GSK3174998 24 mg (Part 1a)
- GSK3359609 80 mg (Part 1b)
- Pembrolizumab 200 mg (Part 1c)

Part 1 will include a GSK1795091 run-in period of 2 weeks (administration on Days 1 and 8) prior to the administration of combination therapy beginning at Day 15. GSK1795091 will continue to be administered weekly up to week 12. Starting at week 12, GSK1795091 will be administered at 3-week intervals to coincide with the administration of the combination partner drug. Three or more participants will be enrolled in each cohort. The total number of participants enrolled into each cohort and dose assignments will be guided by safety information (Protocol Section 5.1.3) from participants receiving the GSK1795091 and study treatment combinations according to N-CRM.

PK/Pharmacodynamic cohorts will be opened at cleared dose levels for that combination (i.e. the most recent investigated dose level that supported dose escalation). Up to 6 participants per dose level may be enrolled into the PK/Pharmacodynamic cohort for each combination.

3.3. STUDY DESIGN FOR THE DOSE EXPANSION PHASE

Following protocol amendment 6, further enrolment was stopped and Part 2 of the study was not open as the development of GSK1795091 was discontinued by GSK.

3.4. SCHEDULE OF EVENTS

Schedule of events can be found in Section 2 of the protocol.

3.5. CHANGES TO ANALYSIS FROM PROTOCOL

No changes.

4. STATISTICAL HYPOTHESES

4.1. PART 1: DOSE ESCALATION

With respect to the primary objectives and endpoints, no specific statistical hypotheses are being tested. The dose escalation part of the study will be focused on the determination of the recommended dose for dose expansion and further exploration, the safety profile, and antitumor activity of the combination of GSK1795091 with GSK3174998, GSK3359609, or Pembrolizumab.

4.2. PART 2: DOSE EXPANSION

Following protocol amendment 6, further enrolment was stopped and Part 2 of the study was not open as the development of GSK1795091 was discontinued by GSK

5. PLANNED ANALYSES

The study will not utilize an Independent Data Monitoring Committee (IDMC). Clinical trial data used in the decisions will be in-stream data only; that is, the data will not necessarily be cleaned in advance of the interim analyses. The following analyses will be performed for this study:

- Interim dose escalation decision analyses during study part 1a, 1b and 1c.
- Primary analysis

- Final analysis
- Note that following protocol amendment 6, further enrolment was stopped and Part 2 of the study was not open as the development of GSK1795091 was discontinued by GSK. Interim futility analyses for part 2a and 2b will not be performed, and a primary analysis will be performed using all data obtained prior to 01July2020.

5.1. INTERIM DOSE ESCALATION DECISIONS

For the dose escalation phase, the Dose Limiting Toxicity (DLT) information along with preliminary safety data, including AEs, changes in laboratory values and other safety parameters, and available PK/pharmacodynamic data will be evaluated by the GSK study team for each dose escalation cohort prior to making dose escalation decisions. Dose escalation (or de-escalation) will proceed as guided by an N-CRM design.

5.1.1. DESCRIPTION OF THE NEUENSCHWANDER-CONTINUAL REASSESSMENT METHOD

The N-CRM model-based design is a Bayesian adaptive dose escalation scheme that assumes a 2-parameter logistic model for the toxicity rate based on dose. It is a modified version of the original Continual Reassessment Method proposed by [O'Quigley,1990]. The N-CRM method is fully adaptive and makes use of all DLT information, and therefore, is expected to locate the target dose level efficiently. In this case, the model will be applied to the dose escalation decision for GSK1795091, which will be performed independently for each combination.

Dose escalation decisions will be held after participants within any given cohort have been observed for at least 6 weeks after starting the study treatment. At the time of each dose escalation decision, the Fixed and Adaptive Clinical Trial Simulator (FACTS [Tessella, Abington, United Kingdom]) will be used to obtain the posterior probabilities for the DLT rate. The N-CRM estimates, for each potential dose, the posterior probabilities that the DLT rate lies in each of four toxicity ranges:

- (0%, 16%) Underdosing
- (16%, 33%) Target toxicity
- (33%, 60%) Excessive toxicity

- (60%, 100%) Unacceptable toxicity

The recommended dose based on the N-CRM model will be the dose with the highest posterior probability of lying in the target toxicity interval with the additional requirement that the sum of the posterior probabilities of the DLT rate lying in the excessive toxicity or unacceptable toxicity range is less than 25%. An updated estimate of the toxicity curve will be provided at the time of each dose escalation meeting. Note that de-escalation as well as escalation is possible using this method. Dose escalation will continue until conditions for either scenario (i) or (ii) are met:

i) Six participants have been treated at the current target dose

AND

For the current dose level, the posterior probabilities of the DLT rate lying within the excessive toxicity interval or within the unacceptable toxicity interval sum to less than 25%

AND

For the next higher dose, the posterior probabilities of the DLT rate lying within the excessive toxicity interval or within the unacceptable toxicity interval sum to greater than 25%.

ii) No doses are usable (i.e., for all doses, the posterior probabilities of the DLT rate lying within the excessive toxicity interval or within the unacceptable toxicity interval sum to more than 25%)

AND

At least 2 DLTs have been observed.

Dose recommendations based on the N-CRM analysis will be used as guidance and the decision about dose will be based on totality of the data. To ensure safety of participants, additional participants may be enrolled at a current dose level at the discretion of the study investigators and sponsor, even though a higher dose is recommended by N-CRM analysis.

5.1.2. Logistic Regression Model for N-CRM

A two-parameter logistic model will be used for N-CRM analysis for dose level selection during the dose escalation phase. This model will estimate the probability of observing a DLT at each

dose level in the study as DLT information becomes available.

The logistic model that used for describing the dose-toxicity relationship is:

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

where p_d is the probability of DLT at dose d, and d_m is a reference dose, and α and β are Bayesian priors.

5.1.3. Displays to be Created for Dose Escalation Review

Evaluation of DLTs for at least three participants who have completed 6 weeks study treatment (including the run-in period) is required prior to determining the dose for the next cohort.

Review of preliminary data will be performed after completion of each dosing cohort in Part 1 using primarily Spotfire and EDC if needed. Preliminary safety and study population data may include a demographic summary, adverse event (AE) summary, AE summary by maximum grade, SAE listing, listing of AEs that are reported to be DLTs, and listing of AEs leading to permanent discontinuation of study treatment.

Further, after the first instance of a DLT and for each subsequent cohort, updated posterior estimates of the probabilities of DLT rate falling in each dose-toxicity range will be provided. The Fixed and Adaptive Clinical Trial Simulator (FACTS) (Version 4.0 or higher) software from Tessella will be used to perform N-CRM analyses.

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

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

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

5.2. PRIMARY ANALYSIS

All planned analyses identified in this SAP will be performed by IQVIA Biostatistics following completion of the following steps:

- All data obtained prior to 01July2020 has been entered into the eCRF.
- For data collected prior to 01July2020, all required critical database cleaning activities have been completed and database lock (DBL) has been declared by Data Management.
- Sponsor authorization of this Statistical Analysis Plan

5.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following completion of the following steps:

- All participants have completed the study as defined protocol amendment 6.
- For data collected after 01July2020, all required critical database cleaning activities have been completed and final database lock (DBL) has been declared by Data Management.

6. ANALYSIS SETS

Agreement and authorization of participants included/excluded from each analysis set will be conducted prior to each planned analysis.

6.1. ALL ENROLLED ANALYSIS SET [ENR]

The All Enrolled Analysis Set includes all participants who sign the ICF to participate in the clinical trial. Participants in this analysis set will be used for the screen failure summary.

6.2. ALL TREATED ANALYSIS SET [TRT]

The All Treated Analysis Set includes all participants who take at least 1 dose of any study

treatment. Analyses of demographic, baseline characteristics, safety and anticancer activity will be based on this analysis set. For analyses and displays based on the TRT, participants will be classified according to actual treatment received.

6.3. PHARMACOKINETIC ANALYSIS SET [PKS]

The Pharmacokinetic Analysis Set will include participants from the TRT who received at least one dose of GSK1795091 treatment, and from whom at least one postdose PK sample was obtained, analyzed, measurable for GSK1795091, and valid (i.e., not affected by protocol deviations or events that warrant exclusion). This analysis set will be the primary population for all PK summaries. For analyses and displays based on the PKS, participants will be classified according to actual treatment received.

6.4. PHARMACODYNAMIC ANALYSIS SET [PDS]

The Pharmacodynamic Analysis Set will include participants in the TRT from whom at least one pharmacodynamic sample was obtained, analyzed and was measurable. This analysis set will be the primary population for pharmacodynamic analyses. For analyses and displays based on the PDS, participants will be classified according to actual treatment received.

7. PARTICIPANT GENERAL CONSIDERATIONS

7.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show relative time from the reference date to start/stop day of assessments and events. Study day will appear in every listing where an assessment date or event date appears.

Reference start date is defined as the day of the first dose of study medication, (Day 1 is the day of the first dose of study medication).

- If the date of the event is on or after the reference date, then:

Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date, then:

Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day and any corresponding durations will be presented based on the imputations specified in Appendix 2: Partial Date Conventions.

7.2. BASELINE

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. For laboratory data, baseline will be the latest non-missing pre-dose value from central lab. If no central lab value is available, the latest non-missing pre-dose value from local lab will be used. If time is not collected and there are multiple assessments on the same day, the mean will be used as the baseline value.

Parameter	Study Assessments Considered as Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
Efficacy				
Disease Assessment	X			Screening
Safety				
Vital Signs	X		X	Day 1 Pre-dose GSK1795091
ECOG	X		X	Day 1 Pre-dose GSK1795091
Physical Examination	X		X	Day 1 Pre-dose GSK1795091 if collected, otherwise, use screening
12-lead ECG	X		X	Mean of triplicate pre-dose GSK1795091 measurements on Day 1
Echocardiogram	X			Screening

Parameter	Study Assessments Considered as Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
Laboratory Assessment	X		X	Day 1 Pre-dose GSK1795091 if collected, otherwise, use screening
Pharmacodynamics				
Pharmacodynamics / Biomarker			X	Day 1 Pre-dose

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

The baseline definition will be footnoted on all change from baseline displays.

7.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. This includes the Treatment Discontinuation Visit (TDV), all TDV data will be summarized under the same visit, regardless of when participants discontinued treatment. Unscheduled measurements will not be included in by-visit summaries but will contribute to the evaluation of best response and best/worst case value where required (e.g. shift table).

In the case of rescreened participants, the latest screening assessments will be used.

Listings will include all assessments, including both scheduled and un-scheduled.

7.4. STATISTICAL TESTS

No statistical comparisons will be conducted for this study. Confidence intervals will be 95%, and all intervals will be two-sided, unless otherwise specified in the description of the analyses.

7.5. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Change from Baseline = Post-Baseline Visit Value – Baseline
- Percentage change from baseline will be summarized as the following:
- Percentage Change from Baseline= 100 x (Post-Baseline Visit Value – Baseline) / Baseline
- Fold change from baseline = (Post-Baseline Visit Value) / Baseline
- Age (years) rounded down to the nearest integer = (Date of informed consent - Date of Birth + 1) / 365.25

If either the Baseline or Post-Baseline Visit Value is missing, Change from Baseline and Fold/Percentage Change from Baseline is set to missing.

7.6. SOFTWARE VERSION

Pharmacokinetic analysis will be conducted using Phoenix WinNonlin Version 8.0 or higher. All analyses will be conducted using SAS version 9.4 or higher.

8. STATISTICAL CONSIDERATIONS

8.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

No adjustments for covariates will be applied to any of the analyses described in this Statistical Analysis Plan.

8.2. MULTICENTER STUDIES

In this multicenter and multi-country study, all centers will be pooled prior to analysis.

Sub-regions will not be defined.

8.3. MISSING DATA

Missing safety data will not be imputed, with the exception of missing baseline for purpose of summarizing grade increase from baseline or change from baseline in terms of normal ranges.

Approaches to missing data for efficacy analyses are described in section 13.

8.4. MULTIPLE COMPARISONS/ MULTIPLICITY

There will be no comparisons conducted between treatment cohorts or study parts for this study.

8.5. EXAMINATION OF SUBGROUPS

- The following subgroups will be explored for selected endpoints:
  - Original vs modified formulation of GSK1795091

9. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

Each treatment cohort (GSK1795091 + GSK3174998, GSK1795091 + GSK3359609, GSK1795091 + Pembrolizumab) will be summarized separately; however, listings will include data from all treatment cohorts. For selected outputs stratified by formulation of GSK1795091, a pooled treatment cohort (GSK1795091 + GSK3174998 or GSK1795091 + GSK3359609 or GSK1795091 + Pembrolizumab) may be presented.

10. DISPOSITION AND WITHDRAWALS

All participants who provide informed consent will be accounted for in this study.

Participants in the TRT analysis set will be considered to have completed the study if they fall into either of the following two categories:

- Participants who experience a DLT (dose limiting toxicity) and complete the treatment discontinuation visit (TDV)
- Participants who complete the 6 week visit and the treatment discontinuation visit (TDV)

Participant disposition and withdrawals from treatment and the study, including primary reason for withdrawal, will be presented for the TRT by cohort, study part and overall. In addition, the number of participants screened, the number of screen failures and the reasons for screen failure will be presented for the SCR by study part and overall. Also, inclusion in all analysis sets will be summarized by cohort, study part and overall for the TRT. A summary of participants screened and treated by country will also be presented for the SCR by study part and overall.

Analysis will be performed by combination partner (separately for each partner and across all partners pooled), dose group, and formulation (Original Formulation, Modified Formulation, or All Formulations).

A listing will be produced to display the information collected in the eCRF regarding patient disposition.

11. PROTOCOL DEVIATIONS

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarized for the TRT by cohort, study part and overall.

- Protocol deviations are recorded in the CTMS, which is considered as the original source document. Deviation category are selected and important deviations are discussed in a monthly deviations meeting with the sponsor and clinical team where important deviations are decided and entered into the CTMS log. Data will be reviewed prior to freezing the database to ensure all important deviations are correctly captured and categorized in the

protocol deviations dataset

- This dataset will be the basis for the summaries and listings of protocol deviations.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan version 2 (26th January 2018).

Important protocol deviations and inclusion in the analysis sets, including reasons for exclusion, will be listed.

12. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the TRT.

No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic and baseline characteristics will be summarized by cohort, study part and overall:

- Age (years) - calculated relative to date of consent
- Age Group (<= 18, 18-64, >=65)
- Sex
- Race (African American/African Heritage, American Indian or Alaskan Native, Asian, Black or African American,Native Hawaiian or Other Pacific Islander, White, Mixed Race)
- Ethnicity
- Child-bearing Potential
- Weight at Baseline (kg)
- Height at Screening (cm)
- BMI (kg/m^2)

All demographic and baseline characteristics data will be listed.

Analysis will be performed by combination partner (separately for each partner and across all partners pooled), dose group, and formulation (Original Formulation, Modified Formulation, or All Formulations).

12.1. DERIVATIONS

- BMI (kg/ m^2) = weight (kg)/ height $(m)^2$
- Creatinine Clearance (CrCl) (mL/min) from serum creatinine will be based on Cockcroft-Gault formula :
- CrCl (male) = ([140-age in years] × weight in kg)/(serum creatinine in mg/dL × 72)
- CrCl (female) = CrCl (male) × 0.85
- If partial dates are present, the following rules will be applied for the calculation of time variables:

  1. If the day is missing the date will be imputed as the first of the month.
  2. If the day and month are missing the date will be imputed as the 1st January.

13. EFFICACY OUTCOMES

Unless otherwise stated, efficacy endpoints will be summarized for the TRT by cohort and study part (where applicable).

For selected efficacy outcomes analysis will be performed by combination partner (separately for each partner and across all partners pooled), dose group, and formulation (Original Formulation, Modified Formulation, or All Formulations).

13.1. PRIMARY EFFICACY

There are no primary efficacy analyses planned for the study.

13.2. SECONDARY EFFICACY

The secondary efficacy analyses involve assessing the antitumor activity of GSK1795091 and its combination partners. These analyses will include the following: objective response rate (ORR), disease control rate (DCR), time to response (TTR), duration of response, progression-free survival (PFS) and overall survival.

Tumor response i.e., complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) will be based on the assessments from the investigators' review of objective evidence (e.g., radiological scan). Overall responses were measured in accordance with the RECIST version 1.1 [Wolchok, 2009; Nishino, 2013].

Lesion assessment method and timing, evaluation of disease, disease progression and response criteria will be conducted according to RECIST (version 1.1) as outlined in Appendix 9 of the protocol.

13.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

13.2.1.1. Best Overall Response

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

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after the first dose at a minimum interval of 8 weeks.
- If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example, if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PD. Alternatively, participants lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

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

13.2.1.2. Objective Response Rate

Objective Response Rate (ORR) is defined as the percentage of participants achieving a confirmed best overall response of CR or PR who received at least one dose of GSK1795091 or its combination partners. ORR will be reported by RECIST v1.1. Participants with Not Evaluable or missing response will be treated as non-responders (i.e. they will be included in the denominator when calculating the rate).

13.2.1.3. Disease Control Rate

Disease control rate (DCR) is defined as the percentage of participants with a confirmed best overall response of CR or PR or at least 12 weeks of SD. For the purpose of analysis, a 2-week window will be allowed, i.e., a SD that is at least 10 weeks after the first dose date will be included in the numerator for DCR calculation. Participants with Not Evaluable or missing response will be included in the denominator when calculating the rate. DCR will be reported by RECIST v1.1.

13.2.1.4. Time to Response

Time to Response (TTR) is defined as the time from the date of first dose (including run-in) to the date of the first documented evidence of response (confirmed PR or CR).

TTR (months) = [Date of onset of response – Date of first dose +1]/30.4375.

If data permits, time to response will be summarized for responders according to RECIST1.1.

13.2.1.5. Duration of Response

Duration of Response (DoR) is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause among participants who achieve an overall response (i.e., a confirmed best overall response of CR or PR). If data permits, DoR will be summarized according to RECIST1.1.

DOR (months) = [Progression/death date (censor date) –Date of first documentation of CR or PR +1]/30.4375.

Censorship: same as PFS censorship (Table D).

13.2.1.6. Progression Free Survival

Progression Free Survival (PFS) is defined as the interval of time (in months) between the date of first dose to the date of disease progression according to clinical or radiological assessment or death due to any causes, whichever occurs earliest. PFS will be reported according to RECIST 1.1.

If there is no adequate baseline assessment, the participants will be censored at their date of first dose. Participants without any adequate post-baseline tumor assessments will be censored at the date of first dose. If the participant does not have a documented date of event, PFS will be censored at the date of the last adequate assessment.

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

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

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

Table A: Censoring Rules

Censoring Rules		
Situation	**Date of Event (Progression/Death) or Censoring**	**Outcome: Event (Progression/Death) or Censoring**
No (or inadequate) baseline tumor assessments and the participant has not died (if the participant has died follow the rules for death indicted at the bottom of the table). An adequate baseline tumor assessment is defined as an assessment where all identified target lesions have diameter recorded.	First Dose Date	Censored

Censoring Rules		
Situation	**Date of Event (Progression/Death) or Censoring**	**Outcome: Event (Progression/Death) or Censoring**
No post-baseline assessments and the participant has not died (if the participant has died follow the rules for death indicted at the bottom of the table)	First Dose Date	Censored
Progression documented between scheduled visits	Date of assessment of progression[1]	Event
No progression *(or death)*	Date of last 'adequate' assessment of response[2]	Censored
New anticancer treatment started *(prior to documented disease progression or death)*.[3]	Date of last 'adequate' assessment of response[2] *(on or prior to starting anti-cancer therapy)*	Censored
Death before first PD assessment (or Death prior to any adequate assessments) without initiating a new anti-cancer therapy	Date of death	Event
Death or progression (whichever is earlier) after more than one missed visit	Date of last 'adequate' assessment of response[2] *(prior to missed assessments)*	Censored

NOTES :

[1] For RECIST v1.1 Criteria: The earliest of (i) Date of radiological assessment showing new lesion (if progression is based on new lesion); or (ii) Date of radiological assessment showing unequivocal progression in non target lesions, or (iii) Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions).

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

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

13.2.1.7. Overall Survival

Overall Survival (OS) is defined as the time from date of first dose of the study treatment (whichever investigational drug administered first) to the date of death for any cause. In the absence of confirmation of death, survival time will be censored at the last date the participant is known to be alive (i.e., at their last known alive date).

The length of OS will be calculated as:

OS (months) = [death date or last known alive date – date of first dose + 1]/30.4375.

Participants lacking data beyond date of first dose will have their survival times censored at date of first dose.

13.2.2. Missing Data Methods for Secondary Efficacy Variables

If the participant starts a new anti-cancer therapy while still on the study and the start date of the new therapy is partial the following rules will be applied:

- If the day of the month is missing and the partial start date falls in the same month as the last dose of study treatment, then assign to earlier of (date of last dose of study treatment+1, last day of month).
- If the day of the month is missing and the partial start date falls in the same month as the participant's last assessment and the participant's last assessment is progressive disease (PD), then assign to earlier of (date of PD+1, last day of month).
- If both rules above apply, then assign to latest of the 2 dates.
- Otherwise, impute missing day to the first of the month.
- If the day of the month and the month is missing and the partial start date falls in the same year as the last dose of study treatment, then assign to earlier of (date of last dose of study treatment+1, 31st December).
- If the day of the month and month is missing and the partial start date falls in the same year as the participant's last assessment and the participant's last assessment is progressive disease (PD), then assign to earlier of (date of PD+1, 31st December).
- If both rules above apply, then assign to latest of the 2 dates.
- Otherwise, impute missing day and month to the 1st January.

In general, if a date is completely missing, no imputation will be performed. Imputed dates will be stored in the time-to-event dataset but will remain partial in any other relevant datasets.

13.2.3. Strategy for Intercurrent Events for Secondary Efficacy Variables

The following will be considered intercurrent events for the analysis of the secondary efficacy endpoints:

- Initiation of an alternative anti-cancer therapy

All recorded disease assessments will be used for the calculation of best confirmed response until the start of a new anti-cancer therapy, regardless of the study treatment status.

13.2.4. Analysis of Secondary Efficacy Variables

13.2.4.1. Best Overall Response

The number and percentage of patients with a best overall response of CR, PR, SD, PD or NE will be presented.

13.2.4.2. Objective Response Rate

Objective response rate and the associated 2-sided 95% exact confidence intervals will be provided separately for each dose using a method based on the binomial distribution. Confirmed response summaries will be provided as per RECIST v1.1.

13.2.4.3. Disease Control Rate

DCR will be summarized in the same way as ORR.

13.2.4.4. Time to Event Endpoints

The time to event endpoints will be summarized using Kaplan-Meier quantile estimates along with 2-sided 95% CIs, with the exception of time to response which, will only be summarized with descriptive statistics (min, max, median, 1st quantile, 3rd quantile).

PFS will be graphically presented using Kaplan-Meier plots.

14. SAFETY OUTCOMES

Unless otherwise specified, all safety outputs will be presented in three sets, one for each combination respectively. For each table for a particular combination, the data will be presented side by side with Part 1 dose level 1, Part 1 dose level 2, and Total.

For selected safety outcomes analysis will be performed by combination partner (separately for each partner and across all partners pooled), dose group, and formulation (Original Formulation, Modified Formulation, or All Formulations).

14.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, with the latest version prior to the database lock.

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study medication.

See Appendix 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case (i.e. treatment emergent).

Listings will include TEAEs and Non-TEAEs. Cytokine or mAB infusion related AEs will also be presented.

14.1.1. ALL TEAEs

An overview summary of AEs, including counts and percentages of participants with any AE, AEs related to any study treatment, AEs leading to permanent discontinuation of study treatment, AEs related to study treatment leading to permanent treatment discontinuation, Grade 3/4 AEs, Related Grade 3/4 AEs SAEs, SAEs related to study treatment, fatal SAEs, and fatal SAEs related to study treatment will be produced.

Severity is classed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE version 4). The maximum grade, as recorded in the eCRF will be used for the summaries. TEAEs starting after the first dose of study medication with a missing

severity will be included in the summaries under grade 'Unknown'.

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

- **Preferred term row**: Participants experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.
- **SOC rows:** Each participant is counted only once at the maximum grade at each SOC level although they may have several different preferred term events within the same SOC.
- **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.

In addition, the frequency and percentage of AEs (all grades) will be summarized and displayed in descending order of total incidence by PT only.

14.1.1.1. Relationship to Study Medication

A "related" TEAE is defined as a TEAE with a reasonable possibility of being related to any study medication as indicated in the eCRF by the investigator. Related TEAE's will be categorized as related to GSK1795091 only, related to combination partner only or related to both. TEAEs with a missing relationship to study medication will be regarded as related to study medication. If a participant reports the same AE more than once, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries. The treatment related AE summaries will be presented by maximum grade by PT only.

14.1.2. COMMON NON-SERIOUS TEAES

A summary table of non-serious adverse events by system organ class and preferred term (number of participants and occurrences) with occurrences >=5% of all subjects within a combination cohort will be generated. No rounding will be applied for including an event in this table, i.e. an event with incidence of 4.9% will not be included.

14.1.3. TEAEs Leading to Discontinuation of Study Medication

TEAEs leading to permanent discontinuation of study medication will be identified from the Adverse Event and Serious Adverse Event eCRF pages where the action taken with the study treatment was selected as "Study treatment withdrawn".

For TEAEs leading to discontinuation of study medication, summaries of incidence rates (frequencies and percentages) by PT only will be prepared. A separate listing of TEAEs leading to discontinuation of study medication will be produced.

14.1.4. TEAEs Leading to Dose Modifications

TEAEs leading to dose reductions and TEAEs leading to dose delays will be identified from the Adverse Event and Serious Adverse Event eCRF pages by the action taken with the study treatment. An AE leading to dose modification is an AE for which either dose reduced or dose delayed was recorded one of the actions taken for the AE. Summary tables of TEAEs leading to dose reductions and dose delays by PT only will be prepared.

14.1.5. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded on the Serious Adverse Events page of the eCRF. A summary of serious TEAEs by PT only will be prepared. In addition SAEs will also be summarized by relationship to GSK1795091 only, relationship to combination partner only and relationship to both. Separate listings of fatal and non-fatal serious TEAEs will also be produced. For common SAEs, a summary table of serious adverse events by system organ class and preferred term (number of participants and occurrences) with occurrences >=5% of all subjects within a combination cohort will be generated. No rounding will be applied for including an event in this table, i.e. an event with incidence of 4.9% will not be included.

14.1.6. Fatal Adverse Events

Fatal TEAEs are those events which are recorded as "Fatal" on the Serious Adverse Events page of the eCRF. A summary of fatal TEAEs by PT only will be prepared.

14.1.7. ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESIs) are defined as events of potential immunologic etiology. AEs will be considered AESIs if indicated by the check box on the Adverse Event and Serious Adverse Event eCRF pages.

The following AESIs will be summarized PT only. In addition, the summary of event characteristics for each category of AESI will also be provided, including number of participants with any event, number of events, number of participants with any event that is serious, number of participants with any event that is related to study treatment, the outcome of the event, maximum NCI-CTCAE grade and the action taken for the event. The percentage will be calculated in two ways, one with number of participants with an event as the denominator and the other with total number of participants as the denominator. The worst-case approach will be applied at participant level for the event outcome and maximum grade, i.e. a participant will only be counted once as the worst case from all the events experienced by the participant. For action taken to an event, participant will be counted once under each action, e.g. if a participant has an event leading to both study treatment discontinuation and dose reduction, the participant will be counted once under both actions. AESIs will be summarized separately as Cytokine-related AEs and Immune-related AEs as collected on the CRF. Cytokine-related AEs

Cardiopulmonary or hemodynamic toxicity starting within 24 hours of study treatment that requires >40% FiO2, vasopressor administration, antiarrhythmic agent or other significant medical intervention. Asystole, as measured by ECG, or bradycardia that is symptomatic and requires medical intervention.

14.1.7.1. Immune-related AEs

Pneumonitis (reported as AESI if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as AESI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as AESI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis

Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis	Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA)	
Endocrine (reported as AESI)		
Type 1 diabetes mellitus (if new onset)		
Hematologic (reported as AESI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Hemolytic Uremic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as AESI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Hepatitis	Autoimmune hepatitis	Transaminase elevations (ALT and/or AST)
Infusion Reactions (reported as AESI for any grade)		
Allergic reaction	Anaphylaxis	
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic (reported as AESI for any grade)		
Autoimmune neuropathy	Guillain-Barré syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as AESI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal (reported as AESI if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as AESI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as AESI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		
Skin (reported as AESI if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		
Other (reported as AESI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

14.2. DEATHS

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

14.3. STUDY MEDICATION EXPOSURE

The number of doses administered of study treatment, the duration of exposure, the cumulative dose, dose intensity and relative dose intensity will be summarized for each of GSK1795091 and its combination partners with mean, median, standard deviation, minimum, and maximum.

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

A horizontal bar graph of duration of treatment in days will be produced. This graph will display overall duration of treatment in days (of any treatment) for each participant, along with the treatment that the participant received, their primary tumor type and the participant's best response.

14.3.1. DERIVATIONS

If the dose date is partial an imputed date will be used for any calculations. If the day is missing the date will be imputed as the first day of the month or the date of first dose, whichever occurs earliest. If the day and month are missing the date will be imputed as 1st January or the date of first dose, whichever occurs earliest.

The duration of exposure to study treatment in days will be calculated according to the following rules:

- If the last dose is prior to week 13 day 1, then Duration of Exposure in Days=Treatment Stop Date – Treatment Start Date + 7.
- If the last dose is week 13 day 1 or later, then Duration of Exposure in Days=Treatment Stop Date – Treatment Start Date + 21.

Cumulative dose is equal to the sum of all actual doses received during the treatment period.

Dose intensity will be calculated as the actual cumulative dose / treatment duration in weeks.Relative dose intensity is calculated as (Dose Intensity / Planned Dose Intensity) x 100.

Where the planned dose intensity is the planned cumulative dose / treatment duration in weeks.

14.4. DOSE LIMITING TOXICITIES

The number and percentage of participants who experience any Dose Limiting Toxicity (DLT) following the first dose of study drug will be presented .

Listing will be provided to provide the participants who experience any Dose Limiting Toxicity (DLT)

14.5. LABORATORY EVALUATIONS

Results from the central laboratory will be included in the reporting of this study for Hematology, Blood Chemistry and Urinalysis. A list of laboratory assessments to be included in the outputs is included in the protocol, appendix 2.

Presentations will use SI Units.

Quantitative laboratory measurements reported as "< X" (i.e. below the lower limit of quantification), or "> X" (i.e. above the upper limit of quantification), will be converted to X/2 or X respectively for the purpose of quantitative summaries, but will be presented as recorded (i.e. as "< X" or "> X" in the listings, where X has been converted into the SI unit).

The following summaries will be provided for laboratory data:

- Increase in NCI-CTCAE grade from baseline will be summarized at each scheduled visit and

for the maximum post-baseline grade increase (for parameters where NCI-CTCAE grades are applicable). The increase to a maximum grade of 3 and the increase to a maximum grade of 4, as well as any grade increase from baseline, will be summarized. Missing baseline grades will be assumed as grade 0. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g. sodium will be summarized as hyponatremia and hypernatremia.

- For lab tests that are not gradable by NCI-CTCAE, 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" categories and the "Increase to High" categories.
- Boxplots of change from baseline by visit (for quantitative measurements)
- Listing of participants with laboratory results outside the normal range
- Listings of all laboratory parameters. Separate listings will be produced for Hematology, Blood Chemistry and Urinalysis (including results for both numeric and categorical parameters).

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 particular visit. Only scheduled visits for a particular lab parameter will be included in the summary of the parameter.

14.5.1. IMMUNOGENICITY

Immunogenicity results of anti-GSK3174998 and anti-GSK3359609 antibody testing will be reported,. The analysis will be based on TRT and will include the following summary tables:

- Summary of Incidence of anti-drug antibodies (ADA): frequency of ADA incidence will be summarized by visit as well as overall ADA incidence (positive at any time).
- Summary of Positive Anti-Drug Antibody Incidence: The number of participants with transient positive or persistent positive ADA will be summarized. Transient positive is defined as single post dose positive or multiple positives at non-sequential time points.

Persistent positive is defined as positive for at least two consecutive visits or a single positive at the last tested visit. If a subject can be classified as both transient positive and persistant positive they will be summarized as persistant positive only.

- If the data allows, the titer will be summarized with quartiles. The highest titer value per participant will be used in the summary. The titer will only be available when it is ADA positive.

The incidence and titer of ADA will be presented at participant level by visit in a listing.

14.5.2. DERIVATIONS

White blood cell differentials (Neutrophils, Lymphocytes, Monocytes, Eosinophils and Basophils) should be converted from absolute values into percentages using the following equation:

$$Differential\ Percentage = ((Differential\ \ Absolute\ Count)/(WBC\ Count))\ \times 100$$

14.5.3. NCI-CTCAE GRADING FOR LABORATORY DATA

Laboratory measurements will be graded using the NCI-CTCAE, Version 4 system as defined in the following link:

https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

14.6. ECG EVALUATIONS

Results from the central ECG (Electrocardiogram) Reading Centre will be included in the reporting of this study.

The following ECG parameters will be reported for this study:

- PR Interval (msec)
- QRS Interval (msec)
- QTcF Interval (msec)

- HR (bpm)
- RR (msec)
- Overall assessment of ECG (Investigator's judgment):
    - Normal
    - Abnormal, Not Clinically Significant (ANCS)
    - Abnormal, Clinically Significant (ACS)

The following summaries will be provided for ECG data:

- Actual and change from baseline by visit (for quantitative measurements)
- QT and QTcF interval increase from baseline to any grade, grade 2 and grade 3 by scheduled timepoint and for the worst post-baseline result according to markedly abnormal criteria (see section 14.6.2 below)
- Incidence of ECG abnormalities by visit
- Incidence of markedly abnormal values at any time post-baseline for PR and QRS
- A figure plotting the baseline QT, and QTcF values and the worst-case post-baseline values. The figure will have reference lines at 450 and 500 msec for both the ordinate and the abscissa axes. There will be diagonal reference lines at equality (i.e. a 45 degree line), at equality plus 30 msec, and at equality plus 60 msec.
- Listing of participants meeting any of the markedly abnormal criteria defined in Section 14.6.2.
- All ECG parameters and findings will be presented in a listing. Where collected in triplicate within a single visit the mean of the replicates will be used for calculating the summary statistics.

14.6.1. ECG Specific Derivations

- Fridericia's Correction (msec)

- $QTcF\ (\text{msec}) = \frac{QT\ (ms)}{\sqrt[3]{RR\ (ms)/1000}}$

14.6.2. ECG MARKEDLY ABNORMAL CRITERIA

Markedly abnormal quantitative ECG measurements will be identified in accordance with the following predefined markedly abnormal criteria:

- Absolute values for QT, and QTcF will be classified as:
  - > 450 - 480 msec (Grade 1)
  - > 480 – 500 msec (Grade 2)
  - > 500 msec (Grade 3)
- Change from Baseline for QT, and QTcF will be classified as:
  - >30 - 60 msec increase from baseline
  - >60 msec increase from baseline
- Absolute values for PR interval will be classified as:
  - > 200 msec
- Absolute values for QRS interval will be classified as:
  - > 120 msec

14.7. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)

- Temperature (^{o}C)
- Weight (kg)
- Height (cm) and BMI (kg/m^2) - listed only.

The following summaries will be provided for vital signs data:

- Actual and change from baseline by visit
- Increase/decrease from baseline to any category, category 2, and category 3by scheduled timepoint and for the worst post-baseline result according to markedly abnormal criteria
- Boxplots of change from baseline by visit (for quantitative measurements)
- Listing of participants meeting markedly abnormal criteria

14.7.1. Vital Signs Markedly Abnormal Criteria

Markedly abnormal quantitative Vital Signs measurements will be identified in accordance with the following predefined markedly abnormal criteria:

Variable	Unit	Low Range	High Range
Increased SBP	mmHg	>140 ≥161 ≥181	<161 <181
Decreased SBP	mmHg		<80
Increased DBP	mmHg	>90 ≥101 ≥111	<101 <111

Variable	Unit	Low Range	High Range
Decreased DBP	mmHg		<50
Increased Heart rate	Bpm	>101 ≥116 ≥131	<116 <131
Decreased Heart rate	Bpm		<45
Change in Heart Rate	Bpm	>20 ≥36 ≥51	<36 <51
Increased Body temperature	˚C	>38.0 ≥38.6 ≥39.1	<38.6 <39.1
Change in Body temperature	˚C	>1.0 ≥1.6 ≥2.1	<1.6 <2.1

15. PHARMACOKINETIC ANALYSIS

All summaries and pharmacokinetic (PK) analyses will be based on the PKS and will be presented by treatment, dose level, formulation (where applicable), and study part. PK concentrations are expected for GSK1795091, GSK3174998, and GSK3359609, and PK

parameters are expected for GSK1795091. Combination partner concentrations (GSK3174998 and GSK3359609 only) will be listed.

Any data excluded from analyses due to protocol deviations that affect PK will be listed but will not be included in summaries. Important protocol deviations or events that could affect PK are changes to the procedures that may impact the quality of the data or any circumstances that can alter the evaluation of the PK.

15.1. PLASMA CONCENTRATION DATA

GSK1795091 plasma concentrations will be summarized by combination partner (separately for each partner and across all partners pooled), dose group, formulation (Original Formulation, Modified Formulation, or All Formulations), and nominal time point using descriptive statistics (n, nBLOQ, mean, standard deviation, geometric mean, geometric %CV and 95% CI for geometric mean, median, minimum, maximum). Subjects who underwent a formulation switch during the study will only be included in the All Formulations summaries. Concentrations that are below the limit of quantitation (BLOQ) will be treated as zero or LLOQ/2 for the computation of non-transformed and transformed descriptive statistics, respectively. If n = 2, only n, median, minimum and maximum will be reported; if n = 1, only n and median will be reported.

The following figures will be presented for GSK1795091 with reference line(s) to represent the LLOQ:

- Median concentration versus nominal time (on continuous scale) figures, generated on linear and semi-logarithmic scales for the time period Day 1 to Day 21. These figures will be prepared by combination partner (separate plots for each partner and separate plots for all partners pooled) and formulation (separate plots for each formulation). Only subjects who received a single formulation throughout the treatment period (Original or Modified) will be included in these plots.
- Median concentration versus nominal time (on categorical scale) figures, generated on linear scale for the full PK assessment period. These figures will be prepared for all combination partners pooled only, separately by formulation (separate plots for each formulation). Only subjects who received a single formulation throughout the treatment period (Original or

Modified) will be included in these plots.

- Individual concentration versus nominal time (on categorical scale) figures, generated on linear scale for the full PK assessment period. Figures will be labeled by combination partner, dose group, and formulation (Original, Modified, or Both). For subjects who underwent a formulation switch during treatment (ie, Both), a vertical dotted line will be added to indicate the time relative time of switch.

A listing of PK blood sample collection times, sampling time deviations, and measured concentrations will be provided for GSK1795091, GSK3174998, and GSK3359609; the listing for GSK1795091 will also indicate the GSK1795091 formulation used. A participant listing of all GSK1795091 concentration-time data for each treatment will be presented.

15.2. PHARMACOKINETIC PARAMETERS

Pharmacokinetic parameters for GSK1795091 will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of Phoenix WinNonlin Version 8.3 or higher, or SAS Version 9.4 or higher.

All calculations of non-compartmental parameters will be based on actual sampling times relative to the dosing time for GSK1795091. Pharmacokinetic parameters listed below will be determined from the plasma concentration-time data, as data permit. All AUCs will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.

Predose NQ values and NQ values prior to the first quantifiable concentration in a concentration-time profile will be set to zero for PK analysis, calculation of descriptive statistics, and individual participant plots. NQ values after the last quantifiable concentration in a profile will be set to missing for PK analysis and individual participant plots, but will be set to zero for calculation of descriptive statistics. If a single NQ value occurs between measurable concentrations in a profile, the NQ should generally be omitted (set to missing) in the derivation of pharmacokinetic parameters, statistical analysis, and the individual subject plots. If there are 2 or more successive embedded NQ values between quantifiable concentrations, the NQ values will be set to missing for calculation of descriptive statistics and set to 0 for individual participant plots. Subsequent quantifiable concentrations in the profile will be set to missing for

calculation of descriptive statistics but included in the individual participant plots. For the derivation of pharmacokinetic parameters, these NQs and any subsequent measurable concentrations will be omitted (set to missing).

The following PK parameters will be calculated.

Parameter	Parameter Description
AUC(0-τ)	Area under the concentration-time curve over the dosing interval (i.e., 0 to 168 hours postdose for GSK1795091), calculated from time zero (predose) to predose of the next dose. This parameter will be estimated on Day 1 (i.e., Day 1-8), Day 15 (i.e., Day 15-22) and Day 57 (i.e., Day 57-64) for GSK1795091. Actual times and associated concentrations at predose of the next dose will be used for calculation of this parameter. If the time deviation from the end of the scheduled dosing interval is greater than 1 calendar day, this parameter and related parameters will be listed but excluded from summaries.
AUC(0-τ)/ Dose	Dose-normalized AUC(0-τ), calculated as AUC(0-τ) divided by dose. This parameter will be estimated for all cases where AUC(0-τ) is estimated.
AUC(0-∞)	Area under the concentration-time curve from time zero (predose) extrapolated to infinity. This parameter will be estimated on Day 1 (i.e., Day 1-8) only, if estimable.
AUC(0-∞)/ Dose	Dose-normalized AUC(0-∞), calculated as AUC(0-∞) divided by dose. This parameter will be estimated when AUC(0-∞) is estimated.
Cmax	Maximum observed plasma concentration, determined directly from the concentration-time data. This parameter will be calculated for all days on which a sample is collected at 10 mins after dosing for GSK1795091, as the concentration measured at that time point. If the sample is taken more than 15 minutes after dosing for GSK1795091, this parameter and related parameters will be listed but excluded from summaries.
Cmax/Dose	Dose-normalized Cmax, estimated as Cmax divided by dose. This parameter will be estimated for all cases where Cmax is estimated.
tmax	The actual time at which Cmax is measured, determined directly from the concentration-time data. This parameter will be estimated for all cases where Cmax is estimated.
λz	Apparent terminal rate constant for GSK1795091, determined by log-linear regression of the terminal phase. The Best Fit method within Phoenix WinNonlin will be used for selection of data points for the regression, followed by manual adjustment if visually warranted.
t1/2	Apparent terminal half-life (h) for GSK1795091, determined as ln2/λz.
CL	Systemic clearance after intravenous dosing (L/h for GSK1795091), calculated as dose divided by AUC(0-∞) on Day 1 and dose divided by AUC(0-τ) on Day 15 and Day 57.
Vss	Volume of distribution at steady state following intravenous dosing (L), calculated as mean residence time (MRT) extrapolated to infinity multiplied by clearance (MRTinf*CL) on Day 1, Day 15, and Day 57

Parameter	Parameter Description
Cpre	Predose concentration (trough concentration at the end of a dosing interval), determined directly from the concentration-time data on all scheduled study days. If the time deviation from the end of the scheduled dosing interval is greater than 1 calendar day, this parameter and related parameters will be listed but excluded from summaries.
Cpre/Dose	Dose-normalized Cpre, estimated as Cpre divided by dose. This parameter will be estimated for all cases where Cτ is estimated.
RAUC(0-τ)	Accumulation ratio for AUC(0-τ), calculated as [{AUC(0-τ) (Day Y) / AUC(0-τ) (Day X)} * 100], where X is the first dosing day for the drug and Y is each subsequent dosing day >X on which AUC(0-τ) is estimated.
RCmax	Accumulation ratio for Cmax, calculated as [{Cmax(Day Y) / Cmax(Day X)} * 100], where X is the first dosing day for the drug and Y is each subsequent dosing day >X on which Cmax is estimated.
RCpre	Accumulation ratio for Cpre, calculated as [{Cpre(Day Y) / Cpre(Day X)} * 100], where Cpre(Day X) is the trough measurement after the first dosing day for the drug and Cpre(Day Y) is the trough measurement on each subsequent dosing day.

The following diagnostic PK parameters will be listed but will not be summarized:

Parameter	Parameter Description
t1/2 Start and Stop time, Interval	The start and stop time and the time interval of the log-linear regression to determine λz will be reported. However, estimates of λz and related parameters will not be excluded from summaries, even if the duration of time over which λz is estimated is < 2 times the subsequently estimated t1/2.
t1/2 N	Number of data points included in the log-linear regression to determine λz. A minimum of 3 data points will be used for determination.
Rsq_adj	Goodness of fit statistic for calculation of λz. If the Rsq_adj value is less than 0.850 (when rounded to 3 significant figures), λz and related parameters [AUC(0-∞), CL, and Vss] will be listed but excluded from summaries.
%AUCex	Percentage of AUC(0-∞)obtained by extrapolation, calculated as [(AUC(0-∞) - AUC(0-last))/ AUC(0-∞) ×100]. If the %AUCex is greater than 20.0% of AUC(0-∞) (when rounded to 3 significant figures), then AUC(0-∞) and related parameters (CL and Vss) will be listed but excluded from summaries.

PK parameters will be summarized by combination partner (separately for each partner and across all partners pooled), dose group, and formulation (Original Formulation, Modified Formulation, or All Formulations) using descriptive statistics (n, mean, standard deviation, median, minimum, maximum, geometric mean, geometric %CV and 95% CI for geometric mean) if n for that level of summarization is ≥ 3 (if n = 2, only n, median, minimum, and maximum will be reported; if n = 1, only n and median will be reported). Geometric mean, geometric %CV and 95% CI for geometric mean will not be calculated for time parameters. Subjects who underwent a formulation switch during the study will only be included in the All Formulations summaries.

Scatter plots (individual values; geometric mean and 95% CI if n > 3) of GSK1795091 PK parameters [Cmax, AUC(0-∞), AUC(0-τ), Cpre, and corresponding dose-normalized parameters for all combination partners pooled] versus dose level (continuous axis) will be generated separately by study day on Days 1, 15, and 57 of Part 1, if sufficient data are available. Only subjects who received a single formulation throughout the treatment period (Original or Modified) will be included in these plots. Both formulations will be shown on the same plot using different symbols. When data are available for both formulations within a dose group, data for the two formulations will be shown slightly offset on either side of the dose level.

A participant listing of individual PK parameters will also be provided; the listing will indicate the GSK1795091 formulation used.

16. PHARMACODYNAMIC / BIOMARKER ANALYSIS

All pharmacodynamic and biomarker analyses will be based on the PDS. All summaries will be presented by cohort and study part unless stated otherwise.

16.1. PHARMACODYNAMIC / BIOMARKER VARIABLES

The following groups of pharmacodynamic and biomarker parameters will be covered in this SAP. All other pharmacodynamic/biomarker variables may be analyzed by GSK and if done would be included in a separate Biomarker RAP.

- Cytokines/Chemokines: IL-10, IL-1β, IL-1Ra, IFNγ, IL-12p70, IL-2, IL-4, IL-5, IL-6, IL-8, GCSF, IP-10, MCP-1, RANTES, TNFα
- WBC count with differentials: neutrophils, lymphocytes, monocytes, eosinophils, basophils
- C-reactive protein (CRP)

16.2. HANDLING OF MISSING DATA FOR PHARMACODYNAMIC / BIOMARKER VARIABLES

Missing pharmacodynamic and biomarker results will not be imputed, however censored results will be imputed for the purpose of the analyses. Censored results are values which cannot be presented numerically because they fall outside the range of quantification (Below the Limit of Quantification (BLOQ) or Above the Limit of Quantification (ALOQ)). For the calculation of change from baseline BLOQ values will be set to the Lower Limit of Quantification (LLOQ) / 2 and ALOQ values will be set to the Upper Limit of Quantification (ULOQ). These same imputation rules will be applied for the calculation of summary statistics of the absolute values where appropriate, as described in section 16.3.

16.3. ANALYSIS OF PHARMACODYNAMIC / BIOMARKER VARIABLES

Pharmacodynamic and biomarker parameters specified in Section 16.1 will be summarized using descriptive statistics (n, n BLOQ, n ALOQ, mean, standard deviation, median, minimum, maximum and geometric mean) by scheduled timepoint if n for that level of summarization is ≥ 3 (if n = 2, only n, n BLOQ, n ALOQ, minimum and maximum will be reported; if n = 1, only n, n BLOQ and n ALOQ will be reported). Absolute and fold change from baseline values will be summarized, however the geometric means will only be calculated for absolute values.

Methods of analysis for absolute pharmacodynamic and biomarker parameters will depend on volume of available data and the proportion of censored results.

- If less than 20% of results are censored, then the mean, standard deviation and geometric mean will be calculated using the traditional approach, with censored values imputed using

the approach described in section 16.2.

- If 20% to 50% of results are censored, then the mean, standard deviation and geometric mean will be calculated using a parametric modelling approach in SAS PROC LIFEREG, using interval censoring. Each value will be defined by a range of possible values. For results which are not censored, the lower and upper limit of the interval will be equal to the recorded result. BLOQ results will be assigned an upper interval limit of the LLOQ and a lower interval limit of 0. ALOQ results will be assigned a lower interval limit of the ULOQ, and the upper interval limit will be missing to signify that any value above the lower interval limit is possible. The mean and standard deviation will be estimated as the intercept and scale parameters respectively of the parametric model, assuming a normal distribution for the parameter result. The geometric mean will be estimated as the back-transformed intercept parameter of the parametric model, assuming a lognormal distribution of the parameter result. Separate analyses will be run for each parameter, treatment group and timepoint and no adjustments for covariates will be made.
- If more than 50% of results are censored, the n, n BLOQ and n ALOQ will be presented only.

If BLOQ values exist within a level of summarization, the minimum and median will not be presented in the summary table. If ALOQ values exist within a level of summarization, the maximum and median will not be presented in the summary table.

As change from baseline variables will not contain censored values after imputation, summary statistics will be calculated using traditional methods.

The following plots will be created for each cytokine respectively:

- Line plot for individual participant level value over time
- Median over time with error bars representing 25 percentile and 75 percentile
- Median fold change from baseline over time (for each timepoint, the fold change is defined as (visit value - baseline value)/baseline value

The visit on the x-axis will be equally spaced ignoring the time scale compared to the first dose so that the early time points can be better viewed from the plot.

The following plot will be created for CRP:

- Median over time with error bars representing 25 percentile and 75 percentile

16.4. ANALYSIS OF PHARMACOKINETIC VERSUS PHARMACODYNAMIC / BIOMARKER VARIABLES

Scatter plots of individual subject Day 1 maximum change-from baseline PD values (for IL-6, TNF-alpha, IL-1RA, IL-10, MCP-1, IP-10, CRP, body temperature, pulse, and systolic blood pressure) versus GSK1795091 Cmax will be prepared. Different symbols will be used to distinguish between GSK1795091 formulations, and trend lines will be overlaid for each formulation.

17. DATA NOT SUMMARIZED OR PRESENTED

The other domains not summarized or presented are:

- Comments
- Local Laboratory Screening Assessments (for hepatitis B and C) and Thyroid function.
- Liver Imaging
- Prior Medical History/Surgeries
- Concomitant medications/surgeries
- Prior/Post-treatment anti-cancer medications
- irRECIST,
- PD other than cytokines and chemokines, biomarker, telephone interview
- Stool,
- Liver events
- ECOG

- PE
- LVEF

These domains and/or variables will not be summarized or presented but will be available in the clinical study database, SDTM and/or ADaM datasets.

18. REFERENCES

1. Lee JJ, Liu DD. A predictive probability design for Phase II cancer clinical trials. Clin Trials. 2008;5:93-106.
2. NCI-CTCAE, Version 4.03: https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
3. Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Statistics Med. 2008; 27:2420-2439.
4. Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res. 2013;19:3936-3943.
5. O'Quigley J, Pepe M, Fisher L. Continual Reassessment Method: A Practical Design for Phase I Clinical Trials in Cancer. Biometrics. 1990; 46:33-48.
6. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, et al. Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. Clin Cancer Res. 2009;15(23):7412-20.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA OUTPUT CONVENTIONS

1. OUTPUT FILE NAMING CONVENTIONS

File names should only consist of uppercase letters, lowercase letters, digits (0 to 9) and underscores. A period should only be used to indicate a separator between the file name and the extension. No spaces, other special characters or punctuation marks are permitted.

As far as possible, output files should be in Rich Text File (RTF) format, although .DOC files are also permitted.

The program, program log and output file name should reflect the type and number of the statistical output. If this is not possible, then the output name should be at least as descriptive as possible. A prefix can be used to distinguish between a Table, Listing and Figure document ('T' for table, 'L' for listing and 'F' for figure). If there is only 1 digit in the number of the table, listing or figure in the place where 2 digits are possible, a leading zero should be added in the file name to make sorting consistent with the sequence (e.g. T14_3_01_1.RTF)

2. PAPER SIZE, ORIENTATION AND MARGINS

The size of paper will be Letter for the United States, otherwise it will be A4.

The page orientation should preferably be landscape, but portrait is also permitted.

Margins should provide at least 1 inch (2.54 centimeters) of white space all around the page, regardless of the paper size.

The number of columns per page (linesize) should be 145 for A4 and 134 for Letter.

The number of rows per page (pagesize) should be 49 for A4 and 51 for Letter.

3. FONTS

The font type 'Courier New' should be used as a default for tables and listings, with a font size of 8. The font color should be black. Single spacing should be used for all text.

Figures should have a default font of "Times Roman", "Helvetica", or "Courier New" with a font size of 12.

4. TABLE AND LISTING OUTPUT CONVENTIONS

General:

- The first row in the body of the table or listing should be blank
- The left hand column should start in column 1. No indenting or centering of the output should occur.
- Rounding should be done with the SAS function ROUND.
- Numbers in tables should be rounded, not truncated.
- Alphanumeric output should be left aligned.
- Numbers should be decimal point aligned.
- Text values should be left aligned.
- The first letter of a text entry should be capitalized.
- The width of the entire output should match the linesize.

Univariate Statistics:

- Table statistics should line up under the N part of the (N=XXX) in the table header. All decimal points should line up. For 'Minimum, Maximum' the comma should line up with the decimal point.
- If the original data has N decimal places, then the summary statistics should have the following decimal places:
- Minimum and maximum: N

- Mean, median and %CV: N + 1
- SD: N + 2

Frequencies and percentages (n and %):

- Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:

```
77 (100.0%)
50 ( 64.9%)
0  (  0.0%)
```

- Percentages will be reported to one decimal place.
- Where counts are zero, percentages of 0.0% should appear in the output.

Confidence Intervals:

- As a rule, confidence intervals are output to one place more than the raw data, and standard deviations and standard errors to two places more than the raw data
- Confidence intervals should be justified so that parentheses displayed on consecutive lines of a table "line up".
- Boundary values should be padded as necessary to accept negative values and to allow alignment of the decimal place. An example is given below:

```
(-0.12, -0.10)
( 9.54, 12.91)
```

Ratios:

- Ratios should be reported to one more decimal place than the original data.

Spacing:

- There must be a minimum of 1 blank space between columns (preferably 2)

Missing values:

- A "0" should be used to indicate a zero frequency.
- A blank will be used to indicate missing data in a participant listing.

5. FIGURE OUTPUT CONVENTIONS

- Figures should be provided in RTF files using the SAS Output Delivery System (ODS), as Computer Graphics Metafile (CGM) formatted graphical output generated by SAS.
- The CGM file itself should contain the title or footer.
- In general, boxes around the figures should be used.

DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

Separate outputs will be generated for each combination partner, which will be identified by a suffix on the output number, which will refer to the study part. For outputs, treatment groups will be represented as follows:

Combination Partner (Study Part)	Cohort Label	Order in TLF
GSK3174998 (A)	50ng GSK1795091 + 8mg GSK3174998	1
	50ng GSK1795091+ 24mg GSK3174998	2
	100ng GSK1795091+ 24mg GSK3174998	3
	150ng GSK1795091+ 24mg GSK3174998	4
	200ng GSK1795091+ 24mg GSK3174998	5
	250ng GSK1795091+ 24mg GSK3174998	6

	Total - Overall (Safety Tables Only)	7
GSK3359609 (B)	50ng GSK1795091+ 24mg GSK3359609	1
	50ng GSK1795091+ 80mg GSK3359609	2
	100ng GSK1795091+ 80mg GSK3359609	3
	150ng GSK1795091+ 80mg GSK3359609	4
	200ng GSK1795091+ 80mg GSK3359609	5
	250ng GSK1795091+ 80mg GSK3359609	6
	Total - Overall (Safety Tables Only)	7
Pembrolizumab (C)	50ng GSK1795091+ 200mg Pembrolizumab	1
	100ng GSK1795091+ 200mg Pembrolizumab	2
	150ng GSK1795091+ 200mg Pembrolizumab	3
	200ng GSK1795091+ 200mg Pembrolizumab	4
	250ng GSK1795091+ 200mg Pembrolizumab	5
	Total - Overall (Safety Tables Only)	7
All Combination Partners Pooled By formulation (D)	50ng GSK1795091 + Partner (Pooled)	1
	100ng GSK1795091 + Partner (Pooled)	2
	150ng GSK1795091 + Partner (Pooled)	3
	200ng GSK1795091 + Partner (Pooled)	4
	250ng GSK1795091 + Partner (Pooled)	5
	Total	6

DL = Dose Level to be determined from N-CRM dose escalation.

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Screening	Screening
Day 1	D1
Day 2	D2

Long Name (default)	Short Name
Day 8	D8
Day 15	D15
Day 16	D16
Day 22	D22
Day 29	D29
Day 36	D36
Day 43	D43
Day 50	D50
Day 57	D57
Day 58	D58
Day 64	D64
Day 71	D71
Day 78	D78
Day 85	D85
Day 106	D106
Day 127	D127
… Continue at 21-day intervals until end of treatment	DXXX
Treatment Discontinuation Visit	TDV
12 Week PFS FU	W12 PFS FU
24 Week PFS FU	W24 PFS FU
… Continue at 12-week intervals until progressive disease	WXX PFS FU

Long Name (default)	Short Name
12 Week SFU	W12 SFU
24 Week SFU	W24 SFU
… Continue at 12-week intervals until death or 2 years after first dose	WXX SFU

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- Study Part (1a, 1b, 1c– where 1 refers to the dose escalation phase, , a the GSK3174998 cohort, b the GSK3359609 cohort and c the Pembrolizumab cohort)
- Treatment group in ascending order of dose level for GSK1795091
- Drug (where applicable - GSK1795091 then combination partner)
- Center-participant ID
- Parameter (where applicable)
- Date (where applicable)
- Timepoint (where applicable)

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE. If start date >= study med start date, then TEAE.
	Partial	If start date < study med start date, then not TEAE. If start date >= study med start date, then TEAE.
	Missing	If start date < study med start date, then not TEAE. If start date >= study med start date, then TEAE.
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE. If stop date >= study med start date, then TEAE.
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE. If stop date >= study med start date, then TEAE.

START DATE	STOP DATE	ACTION
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE. If stop date >= study med start date, then TEAE.
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE. If stop date >= study med start date, then TEAE.
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT/POST MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior. Otherwise: If start date <= end of GSK1795091 treatment + 1 week, or and start date <= end of combination partner treatment + 3 weeks, assign as concomitant. Otherwise assign as post treatment.
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior. Otherwise: If start date <= end of GSK1795091 treatment + 1 week, or and start date <= end of combination partner treatment + 3 weeks, assign as concomitant. Otherwise assign as post treatment.
	Missing	If stop date is missing, could never be assumed a prior medication. If start date <= end of GSK1795091 treatment + 1 week, or and start date <= end of combination partner treatment + 3 weeks , assign as concomitant. Otherwise assign as post treatment.

START DATE	STOP DATE	ACTION
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If start date <= end of GSK1795091 treatment + 1 week, or and start date <= end of combination partner treatment + 3 weeks, assign as concomitant. Otherwise assign as post treatment.
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior. If start date <= end of GSK1795091 treatment + 1 week, or and start date <= end of combination partner treatment + 3 weeks, assign as concomitant. Otherwise assign as post treatment.

START DATE	STOP DATE	ACTION
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication. If start date <= end of GSK1795091 treatment + 1 week, or and start date <= end of combination partner treatment + 3 weeks, assign as concomitant. Otherwise assign as post treatment.
Missing	Known	If stop date < study med start date, assign as prior. Otherwise assign as concomitant.
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior. Otherwise assign as concomitant.
	Missing	Assign as concomitant.

Electronic Signature Manifestation

This page is a manifestation of the electronic signature(s) used in compliance with the organization's electronic signature policies and procedures.

Signer Full Name	Meaning of Signature	Date and Time
PPD	Document Approval (I certify that I have the education, training and experience to perform this task)	23 Dec 2020 16:11:25 UTC
PPD	Document Approval (I certify that I have the education, training and experience to perform this task)	23 Dec 2020 16:14:20 UTC
PPD	Document Approval (I certify that I have the education, training and experience to perform this task)	23 Dec 2020 16:15:58 UTC
PPD	Document Approval (I certify that I have the education, training and experience to perform this task)	23 Dec 2020 16:21:02 UTC
PPD	Document Approval (I certify that I have the education, training and experience to perform this task)	23 Dec 2020 16:23:17 UTC
PPD	Document Approval (I certify that I have the education, training and experience to perform this task)	23 Dec 2020 16:30:29 UTC
PPD	Document Approval (I certify that I have the education, training and experience to perform this task)	23 Dec 2020 17:19:51 UTC