Statistical Analysis Plan

Study ID: 207675

Official Title of Study: Reporting and Analysis Plan for a phase I, open-label, dose-escalation study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of GSK3368715 in participants with solid tumors and DLBCL

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Title	:	Reporting and Analysis Plan for a phase I, open-label, dose-escalation study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of GSK3368715 in participants with solid tumors and DLBCL
Compound Number	:	GSK3368715
Effective Date	:	Refer to Document date

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the abbreviated Clinical Study Report for Protocol 207675.
- This assumed CSR is abbreviated given the study was halted early.
- This RAP is intended to describe planned safety, tolerability, PK, and efficacy analyses required for the study.

RAP Author(s):

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1. INTRODUCTION

This RAP is intended to describe planned safety, tolerability, pharmacokinetics (PK), and efficacy analyses to be performed in support of the Clinical Study Report for GSK Protocol 207675 Amendment 3, dated 05DEC2019.

Protocol Revision Chronology:		
Version 01	02-MAY-2018	Original
Version 02 (Amendment 1)	12-JUL-2018	Changed included: - Modified DLT definitions. - Changes to inclusion criteria. - Incorporation of a hold of study drug for most related Grade 3 adverse events with possible re-start at reduced dose level for thrombocytopenia, anemia, diarrhea, nausea/vomiting, and all other non-hematologic toxicities. - Incorporation of discontinuation of study drug for related Grade 4 adverse events of any duration (excluding most lab abnormalities).
Version 03 (Amendment 2)	22-FEB-2019	Changes included: - Changes and clarifications made in the Schedule of Activities Tables. - Update to CTCAE version 5. - Minor change to inclusion and exclusion criteria Addition of higher dose strength capsules
Version 04 (Amendment 3)	05-DEC-2019	Changes included: - Updated clinical safety guidelines, clinical pharmacology, and the risks/mitigation strategy following the temporary pause in enrolment due to venous thromboembolic events (VTE) that have been observed in the dose escalation phase of the study. Also, the risk of biopsy collection has been added to the benefit/risk assessment table. - Changes to exclusion criteria. - Addition to allowed anti-coagulation therapy. - Addition of exploratory coagulation markers and minor changes to other exploratory biomarkers being collected in the dose escalation phase of the study (Part 1). - Changes and clarifications made in the Schedule of Activities Tables - Changes to DLT and stopping/exclusion criteria for QRS and VTEs, and update to the telemetry assessment. - Addition of food effect cohort into Part 1. - Addition of tablet formulation.

		- Further clarifications added to the sample size determination section. - Addition of albumin in the clinical labs table (Table 9, Appendix 2). - Addition of guidelines of management of toxicity for VTEs in Appendix 12 - Addition of Appendix 13 (Khorana score) - Administrative changes made throughout the document.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

The Dose Escalation Committee (DEC) evaluated the DL100mg cohort and deemed it safe, but upon review of the cumulative safety, efficacy, PK and PD data, GSK decided that no further enrolment will take place on the study. As a result, all analyses corresponding to Part 2, as well as the Exploratory Objectives for both Part 1 and Part 2, will not be performed. Below is the list of analyses that will not be performed:

- There will be no food effect sub-study analysis. Therefore, one of the secondary objectives from Part 1 analysis will not be performed.
- There will be no Part 2 Dose Expansion cohort. Thus, all analyses which support characterization of primary and secondary objectives for the Part 2 cohort (objective response rate analysis, progression-free survival incidence, severity of adverse events, and evaluation of PK parameters) will not be performed.
- Recommended Phase 2 Dose (RP2D) Analysis will not be performed.
- Interim futility analysis (IFA) will not be performed.

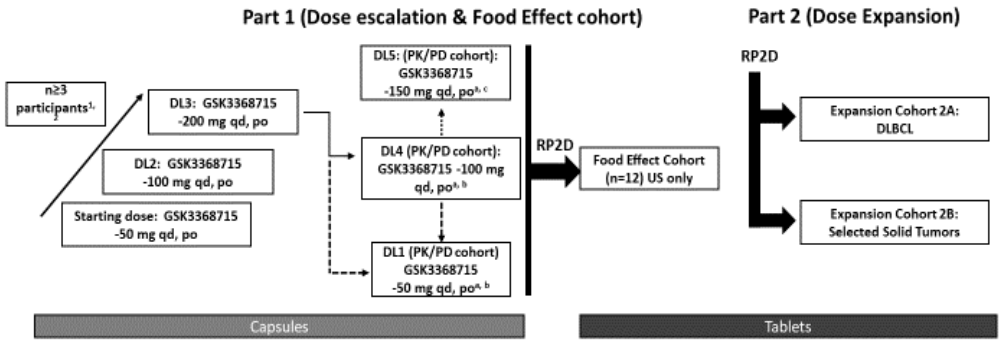
2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Part 1: Dose Escalation	
Primary Objective	**Primary Endpoints**
• Determine RP2D and schedule of GSK3368715 administered orally to participants with advanced stage solid tumors	• Incidence of DLT • Incidence and severity of adverse events
Secondary Objectives	**Secondary Endpoints**
• Evaluate the preliminary clinical activity of GSK3368715	• Best overall response
• Characterize the PK of GSK3368715	• PK parameters (Cmax, Tmax, AUC, and others)
Part 2: Dose Expansion	
Primary Objective	**Primary Endpoint**
• Evaluate the preliminary clinical activity of GSK3368715	• Objective response rate (ORR)

Secondary Objectives	Secondary Endpoints
• Characterize the safety of GSK3368715 administered at the RP2D and schedule to participants with DLBCL, pancreatic cancer, NSCLC, and bladder cancer	• Incidence and severity of adverse events
• Further evaluate the clinical activity of GSK3368715	• Progression-free survival (PFS)
• Characterize the PK of GSK3368715	• PK parameters (Cmax, Tmax, AUC, and others)
Part 1 and Part 2	
Exploratory Objectives/Endpoints	
• Evaluate time to response (TTR), duration of response (DOR) and overall survival (OS)	
• Evaluate changes in PD biomarkers relevant to define the molecular mode-of action of GSK3368715	
• Investigate biomarkers such as, but not restricted to, MTAP deficiency and CDKN2A gene deletion, as potentially predictive of sensitivity or resistance to GSK3368715	
• Characterize the relationship between PK, PD, and clinical activity of GSK3368715	
• Evaluate the relationship of pharmacogenetic profile in host DNA and response to GSK3368715 therapy	
• Determine the impact of GSK3368715 on function and health-related quality of life	
• Determine the amount of GSK3368715 excreted in urine from subjects in the PK/PD expansion cohorts	
• Characterize the metabolic profile of GSK3368715 (in the PK/PD expansion cohorts	

2.3. Study Design

Overview of Study Design and Key Features



a. Participants with advanced/refractory solid tumors.
b. Under protocol amendment 03, enrollment will resume in the 100 mg PK/PD cohort and the 50 mg PK/PD cohort.
c. Dose escalation will be limited to 50 mg increments.

Design Features	• The study includes two phases: Part 1 Dose Escalation and Part 2 Dose Expansion. • Dose escalation use Neuenschwander continual reassessment method (N-CRM). • Cohorts will be expanded at the first instance of a ≥ Grade 2 drug-related non-hematological toxicity. • Every dose level will enroll a minimum of 3 and a maximum of 12 subjects. • Part 1 was planned to enroll up to 40 patients with relapsed/refractory solid tumors. Approx. 30 subjects for DLT evaluation and 10 subjects for PK/PD/Biomarker cohort(s) at a dose of or near MTD/RP2D. • Dose Escalation Committee (DEC): (i) will review all available data, including safety, PK and PD data from current and prior cohorts, (ii) can halt or reduce the GSK3368715 dose based on clinical judgement at any time during the trial, and (iii) can recommend alternative schedule(s) if emerging data suggest that continuous daily dosing will result in excessive toxicity or limited efficacy. Refer to Section 4.1.4 in protocol for the detailed descriptions of the DEC. • Maximum-tolerated Dose (MTD): The highest GSK3368715 dose that emerges from the evaluation of safety-, PK-, and PD-data guided by the N-CRM statistical design during the DLT evaluation period that does not produce unacceptable toxicity. • Recommended Phase 2 Dose (RP2D): Equivalent with the MTD or a lower GSK3368715 dose that provides adequate PK exposure and biologic activity with superior tolerability.

Overview of Study Design and Key Features	
	• Part 2 was planned to enroll up to 141 patients. Specifically, Cohort 2A was planned to enroll up to 36 DLBCL participants. Cohort 2B was planned to enroll up to 35 participants for each indication of pancreatic cancer, NSCLC, and bladder cancer. • In both expansion cohorts, MTAP proficient and deficient participants were to be enrolled. • Participants may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent.
Dosing	• The starting dose of GSK3368715 is 50 mg, qd, po. • At the time of each dose-escalation decision, the dose that has the highest posterior probability of DLT lying in the target toxicity range (≥16% and <33%) with the constraint of posterior probability falling to unacceptable/excessive toxicity being less than 25% will be the model-recommended dose for the next cohort. • The dose will not increase by more than half-logarithmical (3.2-fold) increments. • Dose de-escalation is also possible. • Based on the emerging data, alternative dosing schedule(s), or combination regimens with novel, active agents and/or with approved oncology therapies may be considered. • Any cohort in Part 1 with two (2) grade 2 venous thromboembolism (VTE) that requires systemic anticoagulation or ≥ grade 3 VTE in up to 6 participants will be considered not cleared and enrolment at this dose level and higher dose levels will be permanently stopped. • Any cohort in Part 1 with ≥3 grade 2 venous thromboembolism (VTE) that requires systemic anticoagulation or Grade ≥3 VTEs out of up to 10 participants will be considered not cleared and enrolment at this dose level and higher dose levels will be permanently stopped. • At 100mg, dose escalation steps will be considered in maximal steps of 50 mg depending on the pharmacodynamic effects and the safety profile observed in previous cohorts, taking into consideration the updated DLT criteria. • Grade 2 venous thromboembolism (VTE) that requires systemic anticoagulation or ≥ grade 3 VTE, regardless of investigator assessed causality, will be considered a DLT during the first 8 (± 1) weeks or until study discontinuation (e.g., disease progression), whichever occurs sooner. • An end of treatment CT image is required if the participant withdraws before the end of the VTE DLT observation period.
Time & Events	• Refer to Table 2: Schedule of Assessments (SoA) in protocol
Treatment Assignment	• The study is open-label and GSK3368715 is the only treatment assignment.
Interim Analysis	• The interim analysis was planned to be conducted separately for Cohorts 2A and 2B. • Timing of the first interim futility analysis: Cohort 2A: When at least 5 participants become evaluable from each of the MTAP defined subgroups.

Overview of Study Design and Key Features	
	Cohort 2B: When at least 5 participants become evaluable from MTAP proficient subgroup within any histology cohort. • The interim futility analysis was planned to be performed every 2-3 months with minimum of 5 additional evaluable participants from the entire Cohort 2A or Cohort 2B. • Within Cohort 2A, one Bayesian hierarchical model was to be used to borrow information between the MTAP defined subgroups. Within Cohort 2B, one Bayesian hierarchical model was to be used to borrow information between the MTAP defined subgroups and between the three indications. • Participants enrolled in Part 1 who were treated at the RP2D of GSK3368715 and have the same disease histology as required for Expansion Cohort 2B were to be included in the analyses as appropriate. • The above interim analyses will no longer be carried out due to the early termination of the study.
Final Analysis	• The study will be considered completed for purposes of a final analysis when 70% of participants enrolled in Part 2 have progressed or died. Due to the early termination during the Dose Escalation (Part 1) phase of this study, final analysis will occur prior to the above definition.

2.4. Statistical Hypotheses / Statistical Analyses

2.4.1. Part 1 Dose Escalation

No specific statistical hypotheses are being tested in Part 1. The primary objective is to determine RP2D.

2.4.2. Part 2 Dose Expansion

The Dose Escalation Committee (DEC) evaluated the DL100mg cohort and deemed it safe, but upon review of the cumulative safety, efficacy, PK and PD data, GSK decided that no further enrolment will take place on the study. As a result, all analyses corresponding to Part 2, as well as the Exploratory Objectives for both Part 1 and Part 2, will not be performed. However, all other Part 1 analyses will be performed.

3. PLANNED ANALYSES

3.1. Interim Analyses

In Part 1, dose escalation meetings will be held to discuss dose escalation decisions after all patients in each dose cohort complete the DLT evaluation period of the first 21 days of intervention. Once all subjects in the DLT evaluation cohort (approx. 30 in total) have completed the first post baseline disease assessment, progressed or permanently discontinued from study treatment, a RP2D analysis will be conducted.

The Dose Escalation Committee (DEC) evaluated the DL100mg cohort and deemed it safe, but upon review of the cumulative safety, efficacy, PK and PD data, GSK decided that no further enrolment will take place on the study. As a result, all analyses corresponding to Part 2, as well as the Exploratory Objectives for both Part 1 and Part 2, will not be performed. However, all other Part 1 analyses will be performed.

3.1.1. Dose Escalation Reviews

The primary driver for the dose escalation decisions in Part 1 will be the incidence rate of DLT and other adverse events (AEs) of each dose cohort. The study uses Neuenschwander Continual Reassessment Method (N-CRM) [Neuenschwander, 2008] to guide dose escalation. An updated posterior estimate of the dose-toxicity curve will also be provided at the time of the dose-escalation meeting and the Dose Escalation Committee (DEC) will review all available data and decide if safe to escalate the dose.

The N-CRM design makes use of a Bayesian logistic regression model relating dose and toxicity and makes use of DLT information from all doses. The N-CRM estimates, for each potential dose, the posterior probabilities that the DLT rate lies in each of four toxicity ranges:

- A dose falls in the **Under-dosing** range if the probability of a DLT at the dose is <16%.
- A dose falls in the **Target** Toxicity range if the probability of a DLT at the dose is ≥16% and < 33%.
- A dose falls in the **Excessive** Toxicity range if the probability of a DLT at the dose is ≥33%, and <60%.
- A dose falls in the **Unacceptable** Toxicity range if the probability of a DLT at the dose is ≥60%.

At the time of each dose-escalation decision, the dose with the highest posterior probability of lying in the Target Toxicity range will be the model-recommended dose for the next cohort. Additionally, the following constraints for the recommended dose will be maintained:

- The posterior probability of the DLT rate lying in the Excessive Toxicity or Unacceptable Toxicity range is less than 25%.
- VTE safety rules
    - Upon re-initiation of enrolment under Protocol Amendment 3, details of a VTE meeting the DLT criteria are given in Section 4.1.3 and in Table 6.

- Upon re-initiation of enrolment under Protocol Amendment 3 at 100mg , dose escalation steps will be considered in maximal steps of 50 mg, depending on the pharmacodynamic effects and the safety profile observed in previous cohorts, taking into consideration the updated DLT criteria.
- Note: GSK3368715 dose de-escalation is also possible using this method.

An updated posterior estimate of the dose-toxicity curve will also be provided at the time of the dose-escalation meeting. Further details about the N-CRM approach are provided in Section 9 of Protocol Amendment 3. Although the N-CRM will be used to recommend the next dosing level, the DEC (i) will review all available data, including safety, PK and PD data from current and prior cohorts, (ii) can halt or reduce the GSK3368715 dose based on clinical judgement at any time during the trial, and (iii) can recommend alternative schedule(s) if emerging data suggest that continuous daily dosing will result in excessive toxicity or limited efficacy. Note: if an alternative schedule is evaluated, the starting dose at the time of a schedule change will be the dose for which the target toxicity level was not exceeded using once daily dosing schedule.

3.1.1.1. Displays to Be Created for Dose Escalation Review

For dose escalation decisions, ongoing data review will be primarily based on Tibco Spotfire Clinical Graphics (web-based data visualization tool). The following three listings will be created by Statistics and Programming group. The analysis will be based on the All-Treated Population.

- Listing of All Adverse Events
- Listing of Any Grade 2 and Above Lab Tests or Any Abnormal Lab Tests if Not Gradable
- Listing of Exposure to GSK3368715

For the first dose escalation meeting, only spreadsheets containing relevant study data will be supplied. For subsequent dose escalation meetings, SDTM datasets will be available and the two listings above may be provided. The Data Surveillance Tool may be used to create data visualizations to facilitate review.

Details of the planned displays are presented in Appendix 10: List of Data Displays.

3.1.2. Recommended Phase 2 Dose (RP2D) Analysis

The Dose Escalation Committee (DEC) evaluated the DL100mg cohort and deemed it safe, but upon review of the cumulative safety, efficacy, PK and PD data, GSK decided that no further enrolment will take place on the study. As a result, all analyses corresponding to Part 2, as well as the Exploratory Objectives for both Part 1 and Part 2, will not be performed. However, all other Part 1 analyses will be performed.

RP2D of GSK3368715 was planned to be determined after review of all available safety-, PK-, PD-, and clinical efficacy data in accordance with the N-CRM design. The RP2D was planned to be equivalent with the MTD or a lower GSK3368715 dose that provides adequate PK exposure and biologic activity with superior tolerability.

3.1.2.1. Displays to Be Created for RP2D Analysis

The Dose Escalation Committee (DEC) evaluated the DL100mg cohort and deemed it safe, but upon review of the cumulative safety, efficacy, PK and PD data, GSK decided that no further enrolment will take place on the study. As a result, all analyses corresponding to Part 2, as well as the Exploratory Objectives for both Part 1 and Part 2, will not be performed. However, all other Part 1 analyses will be performed.

3.1.3. Interim futility analyses (IFA) Analyses

The Dose Escalation Committee (DEC) evaluated the DL100mg cohort and deemed it safe, but upon review of the cumulative safety, efficacy, PK and PD data, GSK decided that no further enrolment will take place on the study. As a result, all analyses corresponding to Part 2, as well as the Exploratory Objectives for both Part 1 and Part 2, will not be performed. However, all other Part 1 analyses will be performed.

3.2. Final Analyses

The Dose Escalation Committee (DEC) evaluated the DL100mg cohort and deemed it safe, but upon review of the cumulative safety, efficacy, PK and PD data, GSK decided that no further enrolment will take place on the study. As a result, all analyses corresponding to Part 2, as well as the Exploratory Objectives for both Part 1 and Part 2, will not be performed. However, all other Part 1 analyses will be performed.

The final Part 1 analyses will be performed after all required database cleaning activities have been completed and Database Release (DBR) and Database Freeze (DBF) have been declared by Data Management.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility	• Study Population
Evaluable	• All participants who have had Week 24 disease assessments, have progressed or died, or permanently discontinued from the study intervention.	
All-Treated	• All participants who received at least one dose of GSK3368715.	• Study Population • Final Efficacy • Safety
Pharmacokinetic (PK)	• Participants in the All-Treated population from whom at least one PK sample was obtained, analysed, and was measurable.	• PK

Refer to Appendix 10: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarized and all protocol deviations, including both important and non-important, will be listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Specifications developed by PAREXEL.

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

A separate listing of all important 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.

There is no Per-Protocol Population for this study. Protocol deviations will not be used to determine membership in any particular study population for this study.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

This is a single-arm, dose escalation and expansion study of GSK3368715. Data will be listed and summarized per the GSK reporting standards whenever applicable. In Part 1 data will be listed and summarized by dose levels.

Treatment Group Descriptions	
Data Displays for Reporting	
Description	Order in TLF
GSK3368715 50mg	1
GSK3368715 100mg	2
GSK3368715 200mg	3

5.2. Reporting Conventions

- Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of subjects with a non-missing value at each particular visit.
- All data are reported according to the dose/regimen initially received by the subject.
- Data will be listed by treatment group, site ID, and subject.
- Planned times relative to investigational product dosing will be used in all summary tables and figures.
- Actual, rather than planned, sampling times will be used in the derivation of PK parameters and in the individual concentration-time plots. Planned times will be used in the descriptive summaries and in mean and median plots. Listings of PK concentration-time data will be done by actual sampling times relative to dosing time.
- Unless stated otherwise, descriptive summaries will include n, mean, standard deviation (SD), median, minimum and maximum for continuous variables and n and percent for categorical variables. Display minimum and maximum in the same precision as data was collected, mean and median using 1 additional decimal place, and SD using 2 additional decimal places.
- This is a multicenter study. Data from all study sites will be integrated and no controlling for site-effect will be considered in the statistical analyses.
- Analyses are to be performed using the SAS System, Version 9.4 or higher. Programs will be imported into HARP and the final output will be produced by running drivers in HARP. Some graphics may be produced using the TSCG (Tibco Spotfire Clinical Graphics) - comprising of S-Plus (R) 7.0.6 or higher.
- Deviations from the analyses in the RAP will be identified in the final CSR.

5.3. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment within 14 days prior to first dose with a non-missing value, including those from unscheduled visits. For laboratory data, baseline will be the latest non-missing pre-dose value from central lab. If there are multiple assessments on the same day, the mean will be used as the baseline value. If a subject has an Unscheduled visit for Day 1, collected on the same date as a scheduled visit for Day 1, the planned Day 1 takes precedence over the Day 1 unscheduled visit.

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

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

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

Parameter	Study Assessments Considered as Baseline		Baseline Used in Data Display
	Screening (within 14 days prior to first dose)	Day 1 (Pre-Dose)	
Efficacy			
Target and non-target lesions	X		Screening visit
Safety			
Laboratory	X	X	Latest up to Day 1
Vital Signs	X	X	Latest up to Day 1
ECG*	X	X	Latest up to Day 1

*Average of triplicate assessments to be used.

5.4. Multiple Assessments

All data will be reported according to the nominal visit date for which it was reported (that is, no integration will be applied to combine multiple visits on the same day or different days during dataset creation). Unscheduled data will only be included in the display sections that report worst-case post-baseline (except for PK parameters). For summaries that collapse data across multiple planned time intervals, select the mean data at each collapsed interval.

If multiple assessments on different days are reported for the same scheduled assessment, then the worst-case assessment for that scheduled assessment will be analysed.

If multiple assessments are reported on the same date for the same scheduled planned time, then the mean of multiple measurements reported for the same date will be analysed.

If a subject has an Unscheduled visit for Day 1, collected on the same date as a scheduled visit for Day 1, the planned Day 1 takes precedence over the Day 1 unscheduled visit.

For ECG data where 3 assessments are collected at each scheduled planned time, the average of the 3 measures will be used for analysis at each scheduled planned time.

Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings.

5.5. Multicentre Studies

Data from all participating centres will be pooled prior to analysis.

It is anticipated that subject accrual will be spread thinly across centres and summaries of data by centre would be unlikely to be informative and will not, therefore, be provided.

5.6. Examination of Covariates, Other Strata and Subgroups

5.6.1. Covariates and Other Strata

All analyses are descriptive or unadjusted. No analyses are planned to adjust for any covariate and prognostic factor.

5.6.1. Examination of Subgroups

For Part 2, the efficacy analyses were planned to be conducted by disease cohort and by MTAP status. However, due to the early termination of the study, this will no longer be performed.

5.7. Multiple Comparisons and Multiplicity

No formal statistical comparison will be performed; therefore, no adjustments for multiple comparisons or multiplicity are planned.

5.8. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
14.3	Appendix 3: Assessment Windows
14.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
14.5	Appendix 5: Data Display Standards & Handling Conventions
14.6	Appendix 6: Derived and Transformed Data
14.7	Appendix 7: Reporting Standards for Missing Data
14.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

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

Study population analyses including analyses of subject's disposition, protocol deviations, populations analysed, demographic and baseline characteristics, prior and concomitant medications, exposure, and disease characteristics at initial diagnosis and at screening, will be based on GSK Core and Oncology Data Standards. Details of the planned displays are presented in Appendix 10: List of Data Displays.

6.2. Subject's Disposition

A summary of subject status and reason for study withdrawal and a summary of treatment status and reasons for discontinuation of study treatment will be presented. Reason for study withdrawal and reason for study treatment discontinuation will be listed separately.

A summary and listing of screening status and screen failures will be provided using the screened population.

Number of subjects by country and site will be summarized, along with a summary of study populations.

6.3. Protocol Deviations

Only important protocol deviations will be summarised and all protocol deviations will be listed. Protocol deviations will be classified as 'important' and 'non-important' based on Protocol Deviation Specifications.

A separate listing of inclusion/exclusion deviations will also be provided.

6.4. Demographic Characteristics

The demographic characteristics (e.g. race, race detail, age, ethnicity, sex, height, and baseline body weight) will be summarized and listed. Age, height, and weight will be summarized using the mean, standard deviation, minimum, median and maximum. Age will be also categorized as ≤18, 19-64, ≥65, per the GSK IDSL standard. The count and percentage will be computed for race, sex, and ethnicity.

In a separate summary, age will be categorized as 18-64, 65-84 and ≥85 using EudraCT standard. Subject-level race detail will be listed.

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6.5. Concomitant Medications

All concomitant medications will be summarized. Concomitant medications will be coded using GSK Drug coding dictionary and summarized. The summary of concomitant medications will show the number and percentage of participants taking concomitant medication by Ingredient. Multi-ingredient products will be summarized by their separate ingredients rather than as a combination of ingredients. Anatomical Therapeutic Chemical (ATC) classification Level 1 (Body System) information will be included in the dataset created but will not appear in the summary.

In the summary of concomitant medications, each participant is counted once within each unique ingredient. For example, if a participant takes Amoxycillin on two separate occasions, the participant is counted only once under the ingredient 'Amoxycillin'. In the summary of concomitant medications, the ingredients will be summarized by the base only.

6.6. Exposure Analysis

Summaries of study treatment exposure will be created. This analysis is described in Section 8.1 'Extent of Exposure'.

6.7. Disease Characteristics

Disease characteristics at initial diagnosis including primary tumor type, histology, histological grade, and time since diagnosis to first dose will be summarized and listed. Also, disease characteristics at screening including staging, measurable disease, metastatic disease, and time since progression to first dose, will be summarized and listed. Metastatic disease characteristics at screening, including time since diagnosis of metastatic disease, and metastatic disease site, will be listed. Disease burden at baseline will also be summarised.

6.8. Prior Anti-Cancer Therapy

Participant-level data describing all prior anti-cancer therapies and cancer-specific surgeries, including the type and duration of therapies, will be provided as listings.

7. EFFICACY ANALYSES

The Dose Escalation Committee (DEC) evaluated the DL100mg cohort and deemed it safe, but upon review of the cumulative safety, efficacy, PK and PD data, GSK decided that no further enrolment will take place on the study. As a result, all analyses corresponding to Part 2, as well as the Exploratory Objectives for both Part 1 and Part 2, will not be performed. However, all other Part 1 analyses will be performed.

Thus, only BOR for Part 1 will be summarized by treatment group: CR, PR, overall response (CR+PR), SD, PD and NE. All other planned analyses which are described below will not be performed. However, overall survival times will be listed and summarised.

7.1. Primary Efficacy Analyses

7.1.1. Endpoint / Variables

Given there are no primary efficacy endpoints for Part 1 of the study and Part 2 analyses are not being performed, no primary efficacy analyses will be performed.

7.2. Secondary Efficacy Analyses

The Dose Escalation Committee (DEC) evaluated the DL100mg cohort and deemed it safe, but upon review of the cumulative safety, efficacy, PK and PD data, GSK decided that no further enrolment will take place on the study. As a result, all analyses corresponding to Part 2, as well as the Exploratory Objectives for both Part 1 and Part 2, will not be performed. However, all other Part 1 analyses will be performed.

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

7.2.1. Summary Measure

A participant-level data listing of BOR will be provided, including the name of the corresponding visit, date of the response assessment, study day, and observed response.

7.2.2. Population of Interest

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

7.2.3. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.2.1 will be summarized using descriptive statistics, graphically presented (where appropriate) and listed.

7.3. Exploratory Efficacy Analyses

The Dose Escalation Committee (DEC) evaluated the DL100mg cohort and deemed it safe, but upon review of the cumulative safety, efficacy, PK and PD data, GSK decided that no further enrolment will take place on the study. As a result, all analyses corresponding to Part 2, as well as the Exploratory Objectives for both Part 1 and Part 2, will not be performed. However, all other Part 1 analyses will be performed.

8. SAFETY ANALYSES

The safety analyses will be based on the All-Treated population, unless otherwise specified.

8.1. Extent of Exposure

Subject level details for extent of exposure to study treatment will be listed. The listing will be sorted by part, disease cohort, site, and subject ID. It will include start and stop dates, scheduled dose, actual dose, and number of days on the study treatment.

The details of the planned displays are provided in Appendix 10: List of Data Displays.

8.2. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs) and Serious (SAEs) will be based on GSK Core Data Standards.

Dose limiting toxicity (DLT) will also be summarized and listed according to GSK Oncology Data Standards.

AEs will be graded by the investigator according to the National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) v5.0. AEs will be coded to the Preferred Term (PT) level using the Medical Dictionary for Regulatory Affairs (MedDRA).

An overview summary of AEs, including counts and percentages of subjects with any AEs leading to dose reductions of GSK3368715 and AEs leading to dose interruptions of GSK3368715 will be produced. Separate listings of fatal serious adverse events (SAEs), non-fatal SAEs, reasons for considering as a SAE, AEs leading to permanent discontinuation of GSK3368715, AEs leading to dose interruptions of GSK3368715, AEs leading to dose reductions of GSK3368715, will be produced.

Non-serious AEs that occurred in strictly 5% or more subjects (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) will be summarized by PT.

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

- **Preferred term row**: Subjects experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.
- **Any event row**: Each subject with at least one AE 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 by descending order of total incidence by SOC and PT. In the SOC row, the

number of subjects with multiple events under the same system organ class will be counted once.

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

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

The details of the planned displays are provided in Appendix 10: List of Data Displays.

8.3. Deaths and Serious Adverse Events

In the event that a subject has withdrawn consent, no data after the withdrawal of consent date from this subject including death is supposed to appear in the database, which should be part of the data cleaning process. All deaths will be summarized based on the number and percentage of subjects. This summary will classify subjects by primary cause of death. A supportive listing will be generated to provide subject-specific details on subjects who died.

A summary of the number and percentage of subjects and the number of occurrences of serious, drug-related serious adverse events will be created.

All SAEs will be tabulated based on the number and percentage of subjects who experienced the event. The frequency and percentage of SAEs will be summarized in descending order of total incidence by PT only. A study treatment-related SAE is defined as an SAE for which the investigator classifies the relationship to study treatment as "Yes". A worst-case scenario approach will be taken to handle missing data, i.e. the summary table will include events with the relationship to study treatment as 'Yes' or missing.

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

- Fatal SAEs
- Non-fatal SAEs

Reasons for AE considered as a SAE will be listed.

8.4. Adverse Events Leading to Dose Modification of Study Treatment

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

- SAEs Leading to Permanent Discontinuation of GSK3368715
- AEs Leading to Dose Interruptions of GSK3368715
- AEs Leading to Dose Reductions of GSK3368715

8.5. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of chemistry laboratory tests and haematology laboratory tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 10: List of Data Displays.

Summaries by visit will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied).

Clinical Laboratory Tests are listed in Table 1.

Table 1 List of Clinical Laboratory Tests

Laboratory Assessments	Parameters
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit RBC Indices: MCV, MCH, %Reticulocytes WBC count with Differential: Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils
Clinical Chemistry	BUN Creatinine Glucose Lipase Potassium Sodium Calcium Amylase AST (SGOT) ALT (SGPT) Alkaline phosphatase Total and direct bilirubin Total protein Albumin
Coagulation	PTT, PT/INR
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)

Other Screening Tests	• Highly sensitive serum or urine Beta human chorionic gonadotropin (βhCG) pregnancy test (as needed for women of childbearing potential) • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody) • Cardiac Troponin I or TroponinT (local standard, no point-of-care assay)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; βhCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; HBsAg = Hepatitis B surface antigen; MCH = mean corpuscle hemoglobin; MCV = mean corpuscle volume; RBC = red blood cells; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cells

Laboratory grades will be reported using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.

Summary of lab values change from baseline by scheduled visits using mean, median, standard deviation, minimum, and maximum will be provided. This will be done separately by chemistry and haematology tests.

Missing baseline grade will be assumed as grade 0. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g. sodium will be summarized as hyponatremia and hypernatremia.

A supporting listing of laboratory data for subjects with any value outside normal range will be provided. This will be done separately by chemistry and haematology tests. A separate listing of laboratory data with character values will also be provided.

Detailed derivation of baseline assessment is specified in Section 5.3.

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

8.5.1. Performance Status

ECOG performance status will be summarized at baseline and post-baseline scheduled visits. Summaries will use frequency and percentage of subjects at each planned assessment time. A summary of change from baseline by scheduled visits will be performed.

8.5.2. ECG

A summary of the number and percentage of subjects who had normal and abnormal (clinically significant and not clinically significant) ECG findings will be displayed by scheduled visits Also a summary of change from baseline in ECG values by visit will be produced.

8.5.3. Vital Signs

Vital signs change from baseline will be summarized by scheduled visit using mean, median, standard deviation, minimum and maximum.

In addition, vital sign values will be categorized as follows:

- Systolic BP (mmHg):
  Grade 0 (<120), Grade 1 (120-139), Grade 2 (140-159) and Grade 3 (≥160)
- Diastolic BP (mmHg):
  Grade 0 (<80), Grade 1 (80-89), Grade 2 (90-99), and Grade 3 (≥100)
- Heart rate (beats/min):
  <60, 60-100, and >100
- Temperature (°C):
  ≤35, 36-37, ≥38

A listing of vital signs with values of potential clinical importance will be provided.

8.5.4. 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 and subjects' partner become pregnant while on the study, the information will be included in the narratives and no separate table or listing will be produced.

9. PHARMACOKINETIC ANALYSES

9.1. Endpoint / Variables

9.1.1. Drug Concentration Measures

Two major metabolites of GSK3368715, GSK3963583 and GSK3983164, have been observed in humans.

Concentration of GSK3368715 and metabolites (GSK3963583 and GSK3983164) in the plasma will be listed for each subject in ng/mL.

Individual plots of concentration over time will be provided for each analyte using actual elapsed time for GSK3368715 and metabolites (GSK3963583 and GSK3983164) in ng/mL.

Summaries of plasma concentration will be produced separately for GSK3368715 and metabolites (GSK3963583 and GSK3983164) in ng/mL. Plasma concentration-time data will be summarized using descriptive statistics (n, mean, SD, median, minimum and maximum) by planned relative assessment time.

Mean and/or median values will be plotted over nominal time. GSK3368715 and metabolites (GSK3963583 and GSK3983164) concentration-time profiles will be overlaid on the same plot once concentrations have been converted to nM concentrations. The molecular weight of GSK3368715 and metabolites (GSK3963583 and GSK3983164) are 366.54 g/mol, 338.49 g/mol and 338.49 g/mol respectively. The concentration in nM will be computed for:

- GSK3368715 as GSK3368715 concentration in ng/mL / molecular weight of 366.54 * 1000

- GSK3963583 as GSK3963583 concentration in ng/mL / molecular weight of 338.49 * 1000

- GSK3983164 as GSK3983164 concentration in ng/mL / molecular weight of 338.49 * 1000.

9.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters including Cmax, Tmax, AUC, AUC0-t, AUC0-tau, AUCinf, t½, λz will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin. All calculations of non-compartmental parameters will be based on actual sampling times and concentrations in ng/mL. Pharmacokinetic parameters listed in Table 2 will be determined from the concentration-time data for GSK3368715 and metabolites (GSK3963583 and GSK3983164), as data permits.

Table 2 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
C_{max}	Maximum observed concentration; determined directly from the concentration-time curve.
T_{max}	Time from first administration to occurrence of C_{max}; determined directly from the concentration-time curve.
C_{τ}	Also referred to as "C_{trough}"; observed concentration at the end of a dosing interval, immediately before the next administration; determined directly from the concentration-time curve.
AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-∞)	Area under the concentration-time curve extrapolated to infinity will be calculated as: AUC = AUC(0-t) + C(t) / lambda_z This will be calculated for Week 1/Day 1 only
AUC(0-τ)	Area under the concentration-time curve from time zero to the predose of the next dose.
λz	Apparent terminal phase elimination rate constant
t½	Apparent terminal half-life will be calculated as: t½ = ln2 / λz
TI	Time invariance $TI = \frac{AUC(0-\tau), Day15}{AUC(0-\infty), Day1}$
AR	Accumulation ratio $AR = \frac{AUC(0-\tau), Day15}{AUC(0-\tau), Day1}$
RCMAXM1	Metabolite to drug Cmax ratio RCMAXM1 = (Cmax of GSK3963583* MW of GSK3368715)/(Cmax of GSK3368715* MW of GSK396358)

Parameter	Parameter Description
RCMAXM2	Metabolite to drug Cmax ratio RCMAXM2 = (Cmax of GSK3983164* MW of GSK3368715)/ (Cmax of GSK3368715 * MW of GSK3983164)
RAUCM1	Metabolite to drug AUC(0-t) ratio RAUCM1 = (AUC(0-t) of GSK3963583* MW of GSK3368715)/(AUC(0-t) of GSK3368715* MW of GSK396358)
RAUCM2	Metabolite to drug AUC(0-t) ratio RAUCM2 = (AUC(0-t) of GSK3983164* MW of GSK3368715)/ (AUC(0-t) of GSK3368715 * MW of GSK3983164)

The parameters which involve derivation of ratios including TI, AR, RCMAXM1, RCMAXM2, RAUCM1 and RAUCM1 will computed by Statistics and Programming.

9.1.3. Statistical Analysis of Pharmacokinetic Parameters

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

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

9.1.3.1. Dose Proportionality

Cmax and AUC (AUC(0-∞), single dose, and AUC(0-τ) or AUC(0-24), steady state), will be plotted as a function of the dose administered. Dose proportionality of AUC and Cmax for GSK3368715 following single dose administration and AUC(0-τ) or AUC(0-24) and Cmax following repeat dose administration will be assessed graphically and using the power model as described below:

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

where a is the intercept and b is the slope.

The power model will be fitted by restricted maximum likelihood (REML) using SAS Proc Mixed. Both the intercept and slope will be fitted as fixed effects. If there is sufficient data, the model may also be fit with the intercept and/or slope as random

effects depending on the ability of the model to converge and on estimation of variance-covariance matrix. The mean slope and corresponding 90% confidence interval will be estimated from the power model.

Part 1 Dose Proportionality Analysis
Endpoint(s)
• Cmax and AUC (AUC(0-∞), single dose, and AUC(0-τ) or AUC(0-24), steady state
Model Specification
• Proc Mixed code for dose proportionality analysis: PROC MIXED data=pkpar; BY paramcd; CLASS subjid; MODEL logpk = logdose / ddfm=kr; RANDOM subjid; RUN;
Model Checking & Diagnostics
• Refer to Appendix 10: Model Checking and Diagnostics for Statistical Analyses.

9.1.4. Population of Interest

The primary PK analyses will be based on the PK Population, unless otherwise specified.

10. BIOMARKER ANALYSES

Biomarker data is being collected, but there will be no biomarker analyses conducted.

11. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

No POPPK analyses will be conducted.

12. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

No pharmacokinetic/pharmacodynamic analyses will be conducted.

13. REFERENCES

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Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: Revised RECIST guidelines (version 1.1). Eur J Cancer. 2009;45:228-247.

Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Statistics Med. 2008;27:2420-39.

14. APPENDICES

14.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

14.1.1. Exclusions from Per Protocol Population

No Per Protocol population is defined and used for this study.

14.2. Appendix 2: Schedule of Activities

14.2.1. Protocol Defined Schedule of Events

Refer to Protocol Section 1.3.

14.3. Appendix 3: Assessment Windows

No assessment window will be applied.

14.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

14.4.1. Study Phases

14.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	• Medication End Date < Study Treatment Start Date
Concomitant	• Study Treatment Start Date ≤ Medication End Date ≤ Study Treatment Stop Date

NOTES:

- Please refer to Appendix 7: Reporting Standards for Missing Data for handling of partially missing dates for concomitant medication.

14.5. Appendix 5: Data Display Standards & Handling Conventions

14.5.1. Reporting Process

Software	
• The currently supported versions of SAS software TSCG will be used.	
Reporting Area	
HARP Server	: US1SALX00259
HARP Compound	: gsk3368715\mid207675
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 & ADaM IG Version 1.1).	
Generation of RTF Files	
• RTF files will be generated upon request.	

14.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics

Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  ○ Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  ○ The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  ○ Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  ○ Unscheduled or unplanned readings will be presented within the subject's listings.

Unscheduled Visits
• Unscheduled visits will not be included in summary tables, except in cases where worst-case post-baseline is calculated. • Unscheduled visits will not be included in figures, unless otherwise specified. • All unscheduled visits will be included in listings.

Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

14.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non-compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to SOP_00000314000: Non-compartmental Analysis of Clinical Pharmacokinetic Data. **Note:** Concentration values will be imputed as per GUI_51487.
ADPC data file	To create ADPC the SDTM PC domain dataset will be merged with the Subject-Level Analysis Dataset (to get demographic information) and with SDTM EX domain (to get reference timepoint date). Reference timepoint date will be populated for both study drug and active metabolite based on study treatment information from SDTM EX domain. To populate analysis values in ADPC (AVAL(C)) adjustments to the PCSTRESN will be done based on imputation rules from "Non-Compartmental Analysis of Pharmacokinetic Data, CPMS Global" document. Total Moiety parameter will be added, along with concentrations of study drug and active metabolite, and derived as the sum of study drug and active metabolite concentrations converted to nM units.
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. **Note:** Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarised graphical displays only. Assign zero to NQ values.
Pharmacokinetic Parameter Derivation	
PK Parameters to be Derived by PK Programmer	The following PK parameters will be derived by the Programmer: C_{max}, T_{max}, and C_{τ}.
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes. Refer to Standards for Handling NQ Impacted PK Parameters.

14.6. Appendix 6: Derived and Transformed Data

14.6.1. General

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 multiple assessments on different days are reported for the same scheduled assessment, then the worst-case assessment for that scheduled assessment will be analysed. • 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.
Study Day
• 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
Change from Baseline
• Change from Baseline = Post-Baseline Visit Value – Baseline • % Change from Baseline= 100 x (Post-Baseline Visit Value – Baseline) / Baseline • If either the Baseline or Post-Baseline Visit Value is missing, Change from Baseline and % Change from Baseline is set to missing
Date of Response
• For post-baseline disease assessments, the date of response (PR or CR) is assigned to the latest date of disease assessment; for other response categories (SD, NE, PD), the date of response is assigned to the earliest date of disease assessments.
Date of New Anti-Cancer Therapy
• Derived as the earliest date of new anti-cancer systemic therapy, radiotherapy or cancer-related surgical procedure. • Missing or partial dates will be imputed for derivation of new anti-cancer therapy following rules specified in Section 14.7.2.1.

14.6.2. Study Population

Extent of Exposure
• Missing treatment stop date will be imputed following rules specified in Section 14.7.2.1. • Daily Oral Drugs ○ Number of days of exposure (duration on study treatment) to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – Treatment Start Date + 1** ○ Participants who were enrolled but did not report a treatment start date will be categorized as having zero days of exposure. ○ The cumulative dose will be based on the formula: **Cumulative Dose = Sum of (Number of Days x Total Daily Dose)** ○ If there are any treatment breaks during the study, exposure data will be adjusted accordingly.

Time since Initial Diagnosis
• Calculated as the number of days from the Date of Initial Diagnosis: o If First Dose Date is missing → Elapse Time = Missing o If Date of Initial Diagnosis is completely/partially missing → Elapse Time = Missing o Otherwise → Elapse Time = First Dose Date – Date of Initial Diagnosis + 1 • To report in months, divide the number of days by 30.4375; to report in weeks divide the number of days by 7; to report in years divide the number of days by 365.25.

14.6.3. Safety

Adverse Events
Duration of AE
• Calculated as the number of days from AE Start Date to AE Stop Date: o AE Start Date = Missing → Elapse Time = Missing o AE Stop Date = Missing → Elapse Time = Missing o Otherwise → Elapsed Time = AE Stop Date – AE Start Date + 1 o To report in months, divide the number of days by 30.4375; to report in weeks divide the number of days by 7; to report in years divide the number of days by 365.25.

14.6.4. Efficacy

Refer to Section 7 for endpoint derivation and information.

14.7. Appendix 7: Reporting Standards for Missing Data

14.7.1. Premature Withdrawals

Element	Reporting Detail
General	• A participant enrolled in Part 1 will be considered to have completed the study if they are DLT-evaluable, i.e.: o they complete screening assessments, at least 21 days of study intervention and the post-intervention follow-up visit, or o they discontinue study intervention before Day 21 due to drug related toxicity. Participants who discontinue study intervention before day 21 or who received less than 75% of the intended dose in the first 21 days for reasons other than study drug related toxicity are not considered to have completed the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

14.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

14.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays. However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study phases or for specific analysis purposes as outlined below.
Adverse Events	• Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings. • The eCRF allows for the possibility of partial dates (e.g., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: o <u>Missing Start Day:</u> ▪ If study treatment start date is missing (i.e. participant did not start study treatment), then set AE start date = 1st of month. ▪ Else if study treatment start date is not missing: If month and year of AE start date = month and year of study treatment start date then

Element	Reporting Detail
	☐ If AE stop date contains a full date and is earlier than study treatment start date, then set AE start date= 1st of month. ☐ Else set AE start date = study treatment start date. Else set AE 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 AE start date = January 1. ▪ Else if study treatment start date is not missing: If year of AE start date = year of study treatment start date then ☐ If AE stop date contains a full date and is earlier than study treatment start date, then set AE start date = January 1. ☐ Else set AE start date = study treatment start date. Else set AE start date = January 1. • Completely missing start dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • Completely or partially missing end dates will remain missing, with no imputation applied. Consequently, duration of such events will be missing.
Concomitant Medications	• Completely missing start dates will not be imputed • Partial start dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If day and month are missing: – If treatment start date is missing (i.e., subject did not start study treatment), a '01' will be used for the day and 'Jan' will be used for the month; – If treatment start date is not missing ▪ If year of start date = year of study treatment start date · If stop date contains a full date which is earlier than the treatment start date, a '01' will be used for the day and 'Jan' will be used for the month; · else study treatment start date will be used ▪ else a '01' will be used for the day and 'Jan' will be used for the month ○ If day is missing: – If treatment start date is missing (i.e., subject did not start study treatment), a '01' will be used for the day; – If treatment start date is not missing ▪ If year and month of start date = year and month of study treatment start date · If stop date contains a full date which is earlier than the treatment start date, a '01' will be used for the day; · else study treatment start date will be used ▪ else a '01' will be used for the day and 'Jan' will be used for the month • Completing missing end dates will not be imputed • Partial end dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If day and month are missing – Earliest of (Dec 31st, date of last contact) will be used

Element	Reporting Detail
	○ If day is missing – Earliest of (last day of the month, date of last contact) will be used
New Anti-Cancer Therapy/ Radiotherapy/ Surgical Procedures for Efficacy Evaluation (e.g., response rate, time to event)	Start dates for follow-up anti-cancer therapy, radiotherapy, and surgical procedures will be imputed in order to define event and censoring rules for progression-free survival, response rate, or duration of response (i.e. start date for new anti-cancer therapy). Dates will only be imputed when a month and year are available but the day is missing. The following rules will be used to impute the date when partial start dates are present on anti-cancer therapy, radiotherapy, and/or surgical procedures dataset[s]: • 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;
Prior Anti-Cancer Therapy/ Radiotherapy/ Surgical Procedures	Start and end dates are generally not imputed. If start or end dates need to be imputed for an analysis (e.g., to calculate duration of prior therapy or elapsed time as covariates for efficacy analyses), following rules will be applied. Imputed dates are not used for summary of anti-cancer therapy or radiotherapy. • If start/end date is completely missing or both day and month are missing, no imputation will be applied • If day is missing for start date, first of the month will be used • If day is missing for stop date, ○ If first dosing date is the first of the month, minimum of (last day of the month, first dosing date) will be used ○ Else minimum of (last day of the month, first dosing date - 1) will be used
Date of initial diagnosis/ Last recurrence/ Last progression	Imputed to derive elapsed time (e.g., time since initial diagnosis, time from last progression); not used for summary of disease characteristics at initial diagnosis • If both month and day are missing, first of January will be used • If only day is missing, first of the month will be used
Treatment end date	• If there is more than one study treatment, imputation of missing treatment end date will be applied to all applicable treatments following rules below and treatment end date is the latest treatment end date across all study treatments. • In general, completely missing end dates are not imputed, with the following exceptions for imputation of missing treatment end date at interim analyses. • For imputation of missing exposure end date at an interim analysis when subjects are still on treatment, the following conventions will be applied:

Element	Reporting Detail
	○ If the missing end date is in the last exposure record, the earliest of: the date of the data cut-off, the date of permanently discontinued from the study treatment, the date of withdrawal from the study, or the death date will be used ○ If the missing end date is not in the last exposure record, treatment start date for the record will be used • The imputed treatment end date will be used to calculate cumulative dose and duration of treatment as specified in Section 14.6.2.

14.8. Appendix 8: Values of Potential Clinical Importance

To identify laboratory values of potential clinical importance, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0) will be used to assign grades for laboratory parameters including clinical chemistry, hematology, liver function tests, QTc (Fridericia's) values, 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.

14.8.1. ECG

The following criteria will be used to flag electrocardiogram (ECG) values that are values of potential clinical importance:

To identify QTc (Fridericia's) values of potential clinical importance, NCI-CTCAE v5.0 will be used to assign grades (see adverse event 'Electrocardiogram QT corrected interval prolonged'). The CRF collects QTcF. Note that there is a slight inconsistency between CTCAE v5.0 and ICH E14 (Absolute QTc interval prolongation). It was decided to align with CTCAE for the oncology standard categories.

ECG Parameter	Potential Clinical Importance (PCI) Range	Unit
Absolute QTcF interval	≥450 to <481 (Grade 1) ≥481 to <501 (Grade 2) ≥501 (Grade 3)	Msec
Increase from baseline QTcF	Increase of ≥31 to ≤60 Increase of >60	Msec

The following criteria will be used to flag other ECG values that are values of potential clinical importance:

ECG Parameter	Potential Clinical Importance (PCI) Range	Unit
Absolute PR interval	<110 (Low) >220 (High)	Msec
Absolute QRS interval	<75 (L) >110 (H)	Msec

14.8.2. Vital Signs

To identify heart rate values of potential clinical importance, NCI-CTCAE v5.0 will be used to assign categories that align with the grades for 'Sinus bradycardia', 'Sinus tachycardia', 'Supraventricular tachycardia', and 'Ventricular tachycardia'.

The following criteria will be used to flag vital sign values that are values of potential clinical importance:

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Absolute Heart Rate	<60 (Low) >100 (High)	bpm

To identify blood pressure values of potential clinical importance, NCI-CTCAE v5.0 will be used to assign categories that align with the grades for 'Hypertension'.

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Absolute Systolic Blood Pressure	≥120 to <140 (Grade 1) ≥140 to <160 (Grade 2) ≥160 (Grade 3)	mmHg
Absolute Diastolic Blood Pressure	≥80 to <90 (Grade 1) ≥90 to <100 (Grade 2) ≥100 (Grade 3)	mmHg

To identify temperature values of potential clinical importance, NCI-CTCAE v5.0 will be used to assign categories that align with the grades for 'Hypothermia' and 'Fever'.

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Absolute Temperature	≤35 (Low) ≥38 (High)	Degrees C

14.9. Appendix 9: Abbreviations & Trademarks

14.9.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
A&R	Analysis and Reporting
BOR	Best Overall Response
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
DBF	Database Freeze
DBR	Database Release
DEC	Dose Escalation Committee
DOB	Date of Birth
DOR	Duration of response
DP	Decimal Places
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IFA	Interim futility analysis
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
MTD	Maximum-tolerated Dose
N-CRM	Neuenschwander continual reassessment method
NSCLC	Nonsmall-cell lung carcinoma
ORR	Objective response rate
OS	Overall survival
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PFS	Progression free survival
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK

Abbreviation	Description
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RP2D	Recommended Phase 2 Dose
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SDTM	Study Data Tabulation Model
SoA	Schedule of Assessments
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
TTR	Time to response

14.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

14.10. Appendix 10: List of Data Displays

14.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.16	N/A
Efficacy	2.1	N/A
Safety	3.1 to 3.24	N/A
Pharmacokinetic	4.1 to 4.2	4.11 to 4.15
Section	**Listings**	
ICH Listings	1 to 30	
Other Listings	31 to 39	

14.10.2. Deliverables

Delivery	Description
DE	Dose Escalation
SAC	Final Statistical Analysis Complete

14.10.3. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.1.	All Treated	ES8	Summary of Subject Status and Reason for Study Withdrawal	ICH E3, FDAAA, EudraCT	SAC
1.2.	All Treated	SD4	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	ICH E3	SAC
1.3.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	SAC
1.4.	Screened	NS1	Summary of Number of Participant by Country and Site ID	EudraCT/Clinical Operations	SAC
1.5.	All Treated	ES11	Summary of Outcome of Adverse Events which Led to Study Withdrawal at Each Study Period/Phase	EudraCT	SAC
Protocol Deviation					
1.6.	All Treated	DV1	Summary of Important Protocol Deviations	ICH E3	SAC
Population Analysed					
1.7.	Screened	SP1A	Summary of Study Populations	IDSL	SAC
Demographic and Baseline Characteristics					
1.8.	All Treated	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	SAC
1.9.	Screened	DM11	Summary of Age Ranges	EudraCT	SAC
Prior and Concomitant Medications					
1.10.	All Treated	MH1	Summary of Past Medical Conditions	ICH E3	SAC
1.11.	All Treated	MH1	Summary of Current Medical Conditions	ICH E3	SAC
1.12.	All Treated	CM8	Summary of Concomitant Medications by Ingredient	ICH E3	SAC
Exposure					
1.13.	All Treated	EX1	Summary of Exposure to Study Treatment	ICH E3	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Disease Characteristics					
1.14.	All Treated	DC1	Summary of Disease Characteristics at Initial Diagnosis	ICH E3	SAC
1.15.	All Treated	DC2	Summary of Disease Characteristics at Screening	ICH E3	SAC
1.16.	All Treated	LA1	Summary of Disease Burden at Baseline	ICH E3	SAC

14.10.4. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Responses					
2.1.	All Treated	RE1a	Summary of Best Response without Confirmation (RECIST 1.1 Criteria)		SAC

14.10.5. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events (AEs)					
3.1.	All Treated	AE5B	Summary of All Adverse Events by System Organ Class and Preferred Term and Maximum Grade	ICH E3	SAC
3.2.	All Treated	AE5B	Summary of All GSK3368715-Related Adverse Events by System Organ Class and Preferred Term and Maximum Grade	ICH E3	SAC
3.3.	All Treated	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT	SAC
3.4.	All Treated	AE3	Summary of Adverse Events Leading to Dose Reductions		SAC
3.5.	All Treated	AE3	Summary of Adverse Events Leading to Dose Interruptions		SAC
Serious Adverse Events					
3.6.	All Treated	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT	SAC
3.7.	All Treated	AE3	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment by Overall Frequency	IDSL	SAC
3.8.	All Treated	AE3	Summary of Drug-Related Serious Adverse Events		SAC
Deaths					
3.9.	All Treated	DTH1a	Summary of Deaths	IDSL Report time to death from last dose (in days) as in the mock	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Laboratory: Chemistry					
3.10.	All Treated	LB1	Summary of Chemistry Changes from Baseline	ICH E3	SAC
3.11.	All Treated	LB18	Summary of Chemistry Grade Changes from Baseline	ICH E3	SAC
3.12.	All Treated	LB3	Summary of Chemistry Changes from Baseline with Respect to the Normal Range	ICH E3	SAC
Laboratory: Haematology					
3.13.	All Treated	LB1	Summary of Haematology Changes from Baseline	ICH E3	SAC
3.14.	All Treated	LB18	Summary of Haematology Grade Changes from Baseline	ICH E3	SAC
3.15.	All Treated	LB3	Summary of Haematology Changes from Baseline with Respect to the Normal Range	ICH E3	SAC
ECG					
3.16.	All Treated	EG1	Summary of ECG Findings	IDSL	SAC
3.17.	All Treated	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL	SAC
Vital Signs					
3.18.	All Treated	VS1	Summary of Change from Baseline in Vital Signs	ICH E3	SAC
Dose Modifications					
3.19.	All Treated	ODMOD1	Summary of Dose Reductions of GSK3368715	ICH E3	SAC
3.20.	All Treated	ODMOD2	Summary of Dose Interruptions of GSK3368715	ICH E3	SAC
3.21.	All Treated	ODMOD8	Summary of Dose Escalations of GSK3368715	If applicable.	SAC
Dose Limiting Toxicity (DLT)					
3.22.	All Treated	DL1	Summary of Dose-Limiting Toxicities during the Determinative Period	ICH E3	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Performance Status					
3.23.	All Treated	PS1A	Summary of ECOG Performance Status	ICH E3	SAC
3.24.	All Treated	PS3A	Summary of Change in ECOG Performance Status from Baseline		SAC

14.10.6. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PK					
4.1	PK	PK01	Summary of GSK3368715 Pharmacokinetic Concentration-Time Data by Dose Level, Cohort and Study Day	Use descriptive statistics (n, mean, SD, median, min and max) by planned relative assessment time; concentrations in ng/mL Note: Separate 100mg dose by Dose Escalation, PK/PD and Combined (Dose Escalation and PK/PD) Cohorts.	SAC
4.2	PK	PK01	Summary of GSK3963583 Pharmacokinetic Concentration-Time Data by Dose Level, Cohort and Study Day	Use descriptive statistics (n, mean, SD, median, min and max) by planned relative assessment time; concentrations in ng/mL Note: Separate 100mg dose by Dose Escalation, PK/PD and Combined (Dose Escalation and PK/PD) Cohorts.	SAC
4.3	PK	PK01	Summary of GSK3983164 Pharmacokinetic Concentration-Time Data by Dose Level, Cohort and Study Day	Use descriptive statistics (n, mean, SD, median, min and max) by planned relative assessment time; concentrations in ng/mL Note: Separate 100mg dose by Dose Escalation, PK/PD and Combined (Dose Escalation and PK/PD) Cohorts.	SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
4.4	PK	PK06	Summary of Derived GSK3368715 Pharmacokinetic Parameters by Dose Level, Cohort and Study Day	PK parameters: Cmax, Tmax, Ctrough, AUC0-t, AUC0-tau, AUCinf, t½, λz, TI and AR determined from the concentration-time data in ng/ml; descriptive summaries: mean, SD, median, min, max, geometric mean & SD, CV%, and 95%CI of log-transformed parameters, if applicable. Note: Separate 100mg dose by Dose Escalation, PK/PD and Combined (Dose Escalation and PK/PD) Cohorts.	SAC
4.5	PK	PK06	Summary of Derived GSK3963583 Pharmacokinetic Parameters by Dose Level, Cohort and Study Day	PK parameters: Cmax, Tmax, Ctrough, AUC0-t, AUC0-tau, AUCinf, t½, λz, TI, AR, RCMAXM1 and RAUCM1 determined from the concentration-time data in ng/ml; descriptive summaries: mean, SD, median, min, max, geometric mean & SD, CV%, and 95%CI of log-transformed parameters, if applicable. Note: Separate 100mg dose by Dose Escalation, PK/PD and Combined (Dose Escalation and PK/PD) Cohorts.	SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
4.6	PK	PK06	Summary of Derived GSK3983164 Pharmacokinetic Parameters by Dose Level, Cohort and Study Day	PK parameters: Cmax, Tmax, Ctrough, AUC0-t, AUC0-tau, AUCinf, t½, λz, TI, AR, RCMAXM2 and RAUCM2 determined from the concentration-time data in ng/ml; descriptive summaries: mean, SD, median, min, max, geometric mean & SD, CV%, and 95%CI of log-transformed parameters, if applicable. Note: Separate 100mg dose by Dose Escalation, PK/PD and Combined (Dose Escalation and PK/PD) Cohorts.	SAC
4.10	PK		Summary Results of Single Dose Proportionality Assessment Using Power Model for GSK3368715		SAC

14.10.7. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PK					
4.11	PK	PK16	Individual GSK3368715 Concentration-Time Plots (Linear and Semi-Log)by Dose Level, Cohort and Study Day	ng/mL	SAC
4.12	PK	PK16	Individual GSK3963583 Concentration-Time Plots (Linear and Semi-Log) by Dose Level, Cohort and Study Day	ng/mL	SAC
4.13	PK	PK16	Individual GSK3983164 Concentration-Time Plots (Linear and Semi-Log) by Dose Level, Cohort and Study Day	ng/mL	SAC
4.14	PK	PK17	Mean Concentration-Time Plots (Linear and Semi-Log) by Dose Level, Cohort and Study Day	GSK3368715 and metabolites (GSK3963583 and GSK3983164) concentration time profiles will be overlaid on the same plot once concentrations have been converted to nM concentrations. Note: Separate 100mg dose by Dose Escalation, PK/PD and Combined (Dose Escalation and PK/PD) Cohorts.	SAC
4.15	PK	PK18	Median Concentration-Time Plots (Linear and Semi-Log) by Dose Level, Cohort and Study Day	GSK3368715 and metabolites (GSK3963583 and GSK3983164) concentration time profiles will be overlaid on the same plot once concentrations have been converted to nM concentrations. Note: Separate 100mg dose by Dose Escalation, PK/PD and Combined (Dose Escalation and PK/PD) Cohorts.	SAC

14.10.8. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC
2.	All Treated	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC
3.	All Treated	SD2	Listing of Reasons for Study Treatment Discontinuation	ICH E3	SAC
Protocol Deviations					
4.	All Treated	DV2	Listing of Protocol Deviations	ICH E3 Report all PDs	SAC
5.	All Treated	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC
Demographic and Baseline Characteristics					
6.	All Treated	DM2	Listing of Demographic Characteristics	ICH E3	SAC
7.	All Treated	DM9	Listing of Race	ICH E3	SAC
Prior and Concomitant Medications					
8.	All Treated	CP_CM3	Listing of Concomitant Medications	IDSL Note: IDSL shell in development. Required for ClinPharm studies instead of a corresponding table. Not required for studies where a table is produced.	SAC
Exposure					
9.	All Treated	OEX3A	Listing of Treatment Exposure to GSK3368715	ICH E3	DE, SAC
Dose Modifications					
10.	All Treated	ODMOD10A	Listing of Dose Reductions	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
11.	All Treated	ODMOD11A	Listing of Dose Interruptions	ICH E3	SAC
Response					
12.	All Treated	RE5	Listing of Responses without Confirmation (RECIST 1.1 Criteria)		SAC
13.	All Treated,	RE12	Listing of Subject Best Response		SAC
Adverse Events					
14.	All Treated	AE8	Listing of All Adverse Events	ICH E3	DE, SAC
15.	All Treated	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC
Serious and Other Significant Adverse Events					
16.	All Treated	AE8	Listing of Fatal Serious Adverse Events	ICH E3	SAC
17.	All Treated	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3	SAC
18.	All Treated	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC
19.	All Treated	AE8	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment	ICH E3	SAC
20.	All Treated	AE8	Listing of Adverse Events Leading to Dose Interruptions of Study Treatment	ICH E3	SAC
21.	All Treated	AE8	Listing of Adverse Events Leading to Dose reductions of Study Treatment	ICH E3	SAC
Dose-Limiting Toxicities					
22.	All Treated	DL3	Listing of Dose-Limiting Toxicities (DLT) During the Determinative Period		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Deaths					
23.	All Treated	DTH3	Listing of Deaths	ICH E3	SAC
All Laboratory					
24.	All Treated	LB5A	Listing of All Chemistry Laboratory Data for Participants with Any Value of Outside Normal Range	ICH E3	SAC
25.	All Treated	LB5A	Listing of All Hematology Laboratory Data for Participants with Any Value of Outside Normal Range	ICH E3	SAC
26.	All Treated	LB14	Listing of Laboratory Data with Character Results	ICH E3	SAC
ECG					
27.	All Treated	EG3	Listing of All ECG Values for Participants with Any Value of Potential Clinical Importance	IDSL	SAC
28.	All Treated	OECG5A	Listing of QTcF Values of Potential Clinical Importance		SAC
Vital Signs					
29.	All Treated	OVT7A	Listing of Vital Signs with Values of Potential Clinical Importance		SAC
Performance Status					
30.	All Treated	PS5A	Listing of Performance Status		SAC

14.10.9. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Disease Characteristics					
31.	All Treated	DC3	Listing of Disease Characteristics at Initial Diagnosis		SAC
32.	All Treated	DC4	Listing of Disease Characteristics at Screening		SAC
33.	All Treated	MD2	Listing of Metastatic Disease at Screening		SAC
Anti-Cancer Therapy					
34.	All Treated	AC6	Listing of Prior Anti-Cancer Therapy	List all prior anti-cancer therapy (but not radiotherapy or surgery)	SAC
35.	All Treated	AC7	Listing of Prior Anti-Cancer Radiotherapy		SAC
Surgical Procedures					
36.	All Treated	OSP3	Listing of Prior Cancer Related Surgical Procedures		SAC
Responses					
37.	All Treated	LA5	Listing of Lesion Assessments (RECIST 1.1 Criteria)		SAC
PK					
38.	PK	PK07	Listing of Pharmacokinetic Concentration-Time Data by Group	IDSL	SAC
39.	PK	PK13	Listing of Derived Pharmacokinetic Parameters by Group	IDSL	SAC